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(21) International Application Number: PCT/SE97/00315 (22) International Filing Date: 25 February 1997 (25.02.97) (30) Priority Data: 9600769-5 28 February 1996 (28.02.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DIMAIO, John [CA/CA]; 12404 Pierre Blanchet Street, Laval, Quebec H1E 4L9 (CA). WANG, Wuyi [CA/CA]; 2297 Frenette, St.-Laurent, Quebec H4R 1M3 (CA). (74) Agents: LINDEROTH, Margareta et al.; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: ISOQUINOLINES USEFUL AS ANALGESICS (57) Abstract The present invention is concerned with compounds which can act as analgesic. More specifically, the analgesic compounds of the invention are peptidomimetic compounds which can bind to opioid receptors.		

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ISOQUINOLINES USEFUL AS ANALGESICS

FIELD OF THE INVENTION

- 5 The present invention is concerned with compounds that can act as analgesic.

BACKGROUND OF THE INVENTION

- 10 Many endogenous peptides of mammalian and amphibian origin bind to specific opioid receptors and elicit an analgesic response similar to classic narcotic opiates. Many different types of opioid receptors have been shown to coexist in higher animals. For example, see W. Martin et al., J. Pharmacol. Exp. Ther., 197, p. 517(1975); and J. Lord et al., Nature(London), 257, p. 495(1977). Three different types of opioid receptors have been identified. The first, μ , shows a differentiating affinity for enkephalin-like peptides. The second, δ , shows enhanced selectivity for morphine and other
20 poly-cyclic alkaloids. The third, κ , exhibits equal affinity for either group of the above ligands and preferential affinity for dynorphin. In general, the μ -receptors seem to be more involved with analgesic effects. The δ -receptors appear to deal with behavioral effects, although the δ and
25 the κ -receptors may also mediate analgesia.

- Each opioid receptor, when coupled with an opiate, causes a specific biological response unique to that type of receptor. When an opiate activates more than one receptor, the
30 biological response for each receptor is affected, thereby producing side effects. The less specific and selective an opiate may be, the greater the chance of causing increased side effects by the administration of the opiate.

In the prior art, opiates, opioid peptides, and analogs thereof, have either failed to demonstrate, or have demonstrated a limited degree of specificity and selectivity for the type of receptor, or receptors, to which they bind.

5 The primary site of action of analgesic opioids is the central nervous system (CNS). Conventional narcotic analgesics are normally quite hydrophobic and thus are extremely well-suited to permeate lipid membranes, such as
10 the blood-brain barrier. Due to this physical capability, analgesics tend to bind with opioid receptors within the central nervous system in the brain. However, they do not necessarily bind with a homogeneous receptor subtype. This binding causes medically undesirable side effects to occur.

15 Opiates can cause serious and potentially fatal side effects. Side effects such as respiratory depression, tolerance, physical dependence capacity, and precipitated withdrawal syndrome are caused by nonspecific interactions with central
20 nervous system receptors. See K. Budd, In International Encyclopedia of Pharmacology and Therapeutics; N.E. Williams and H. Wilkinson, Eds., Pergamon: (Oxford), 112, p.51 (1983). Therefore, opioid analgesics acting principally through opioid receptors in the peripheral nervous system
25 would not be expected to cause similar unwanted side effects as those side effects associated with opioid analgesics affecting the central nervous system.

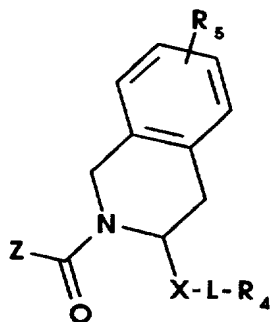
To date, one of the few classes of agents known to exert
30 peripheral analgesic effects are non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, and ketorolac. These agents do not interact with opioid receptors but are known to inhibit cyclooxygenase and attenuate prostaglandin synthesis. These weak analgesics do
35 not have centrally mediated side effects, but they can cause

other side effects such as ulcerations of the gastro-intestinal tract.

- 5 There is therefore a need for opioid analgesic that can substantially affect the peripheral nervous system and therefore overcome some of the disadvantages of conventional opiates by substantially preventing unwanted side effects from occurring.
- 10 There is therefore a need to provide opioid-like peptides which act peripherally but substantially avoid the unwanted side effects associated with conventional peripherally acting analgesics.
- 15 There is also a need for opioid analgesic that can be administered orally.

SUMMARY OF THE INVENTION

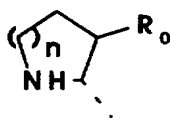
5 The present invention provides analgesic compounds of general formula (I):



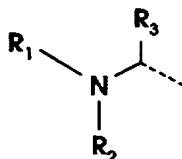
(I)

10 wherein;

Z is



15 or



wherein;

20 n is 1 or 2, and R₀ is C₆₋₁₂ aryl or C₇₋₁₈ aralkyl;

R₁ is selected from the group consisting of hydrogen; -NH-C₁₋₆ alkyl; C₁₋₆ alkyl; C₆₋₁₂ aryl; C₇₋₁₈ aralkyl; arginyl; and R₃₀NHC(=NH)-, wherein, R₃₀ is hydrogen, C₆₋₁₂ aryl, C₇₋₁₈ aralkyl, or C₁₋₆ alkyl;

25

R_2 is hydrogen; C_{1-6} alkyl; or OH;

R_3 is C_{6-12} aryl; or C_{6-18} aralkyl;

5

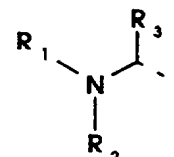
R_4 is C_{6-12} aryl; C_{7-18} aralkyl; or C_{1-12} alkyl;

R_5 is C_{1-6} alkyl; hydrogen; OH; halogen; SH; NO_2 ; NH_2 ;

-NH- C_{1-6} alkyl; $NH_2C(=NH)-$; $NH_2C(=NH)-NH-$; $-COOR_{31}$, wherein, R_{31}
10 is hydrogen, or C_{1-6} alkyl;

X is $-CH_2NHC(O)-$; $-CH_2NHC(O)O-$; $-C(O)NH-$; or $-CH_2NH-$;

L is a C_{1-12} alkyl chain which can be substituted with at least
15 one substituent selected from the group consisting of cyclic
moiety; C_{1-6} alkyl; OR_{31} wherein, R_{31} is hydrogen or C_{1-6} alkyl;
 SR_{32} wherein, R_{32} is hydrogen or C_{1-6} alkyl; $-NHC(O)R_{33}$ wherein,
 R_{33} is C_{6-12} aryl, C_{7-18} aralkyl or C_{1-6} alkyl; $-OC(O)R_{34}$ wherein,
 R_{34} is hydrogen, C_{6-12} aryl, C_{7-18} aralkyl, C_{1-6} alkyl, $-NHR_{35}$
20 wherein, R_{35} is hydrogen, C_{6-12} aryl or C_{1-6} alkyl; and NR_6R_7 ,
wherein each of R_6 and R_7 is independently hydrogen or C_{1-6}
alkyl;



with the proviso that when R_5 is hydrogen, Z is
25 X is $-C(O)NH-$, or $-CH_2NH-$; that L is a C_{1-12} alkyl chain
substituted with at least one substituent selected from the
group consisting of cyclic moiety; C_{1-6} alkyl; OR_{31} wherein, R_{31}
is hydrogen or C_{1-6} alkyl; SR_{32} wherein, R_{32} is hydrogen or C_{1-6}
alkyl;

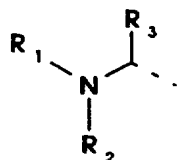
-NHC(O)**R**₃₃ wherein, **R**₃₃ is C₆₋₁₂ aryl, C₇₋₁₈ aralkyl or C₁₋₆ alkyl;
 -OC(O)**R**₃₄ wherein, **R**₃₄ is hydrogen, C₆₋₁₂ aryl, C₇₋₁₈ aralkyl, C₁₋₆
 alkyl, -NHR₃₅ wherein, **R**₃₅ is hydrogen, C₆₋₁₂ aryl or C₁₋₆ alkyl;
 and NR₆R₇, wherein each of **R**₆ and **R**₇ is independently hydrogen
 5 or C₁₋₆ alkyl.

The invention also provides for pharmaceutically acceptable
 compositions comprising those compounds, for use in the
 treatment of pain.

10

The invention further provides the use of compound of formula
 (I) wherein that **L** is a C₁₋₁₂ alkyl chain which can be
 substituted with at least one substituent selected from the
 group consisting of cyclic moiety; C₁₋₆ alkyl; OR₃₁ wherein, **R**₃₁
 15 is hydrogen or C₁₋₆ alkyl; SR₃₂ wherein, **R**₃₂ is hydrogen or C₁₋₆
 alkyl; -NHC(O)**R**₃₃ wherein, **R**₃₃ is C₆₋₁₂ aryl, C₇₋₁₈ aralkyl or C₁₋₆
 alkyl; -OC(O)**R**₃₄ wherein, **R**₃₄ is hydrogen, C₆₋₁₂ aryl, C₇₋₁₈
 aralkyl, C₁₋₆ alkyl, -NHR₃₅ wherein, **R**₃₅ is hydrogen, C₆₋₁₂ aryl
 or C₁₋₆ alkyl; and NR₆R₇, wherein each of **R**₆ and **R**₇ is
 20 independently hydrogen or C₁₋₆ alkyl; for the manufacture of
 peripheral analgesic for the treatment of pain.

Detailed description of the invention



25 **Z** is preferably $\begin{array}{c} \text{R}_1 \quad \text{R}_3 \\ \diagdown \quad \diagup \\ \text{N} \\ \diagup \\ \text{R}_2 \end{array}$, wherein each of **R**₁, **R**₂, and **R**₃ are
 as defined above.

R₁ is preferably hydrogen; NH₂C(=NH)-; or C₁₋₆ alkyl.

R₁ is more preferably hydrogen; NH₂C(=NH)-; or -CH₃.

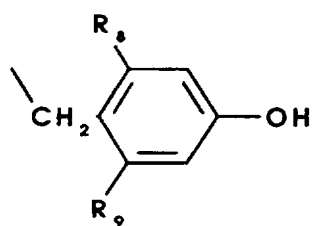
30 **R**₁ is most preferably hydrogen.

R_2 is preferably hydrogen or $-CH_3$.

R_2 is more preferably hydrogen.

- 5 R_3 is preferably $-CH_2-C_6H_2R_8R_9-$, or $-CH_2-HOC_6HR_8R_9$, wherein each of R_8 and R_9 is independently $-CH_3$ or hydrogen.

R_3 is most preferably



10 ; wherein R_8 and R_9 are as defined above.

R_8 and R_9 are preferably CH_3 .

- 15 X is preferably $-C(O)NH-$; or $-CH_2NH-$.

X is more preferably $-C(O)NH-$.

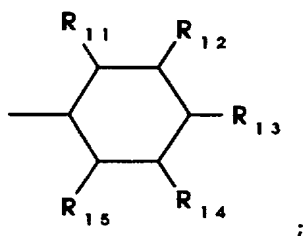
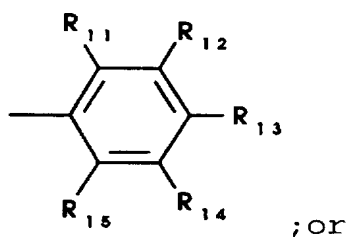
L is preferably $-(CH_2)_{1-3}-CHR_{10}-(CH_2)_{1-3}-$, wherein R_{10} is OH , or NH_2 .

- 20 L is more preferably $-(CH_2)-CHR_{10}-(CH_2)-$, wherein R_{10} is OH , or NH_2 .

L is more preferably $-(CH_2)-CHOH-(CH_2)-$.

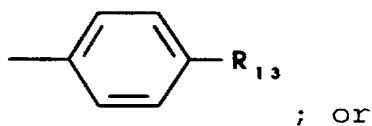
R_4 is preferably:

- 25 C_{1-12} alkyl;

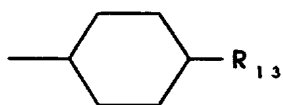


- 5 wherein each of **R₁₁**, **R₁₂**, **R₁₃**, **R₁₄**, and **R₁₅** is independently CH₃, hydrogen, halogen, OH, SH, NH₂, or NO₂.

R₄ is more preferably: -CH₃; -C(CH₃)₃; -CH(CH₃)₂;

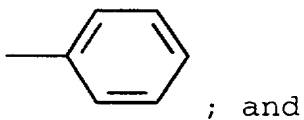


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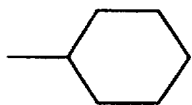


wherein **R₁₃** is as defined above.

R₄ is most preferably selected from the group consisting of:



15



The compounds of the present invention are preferably selected from the group consisting of :

2-R-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture) **compound #1**;

2-R-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) **compound #1A**; 2-R-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **Compound #1B**; 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-7-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture) **compound #2**; 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt (racemic mixture) **compound #3**; 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt (fast isomer) **compound #3A**; 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt (slow isomer) **compound #3B**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture) of **compound #4**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast

isomer) of **compound # 4A**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow

5 isomer) **Compound #4B**;

S-2-(2-Amino-3-(hydroxy-phenyl)-S-1,2,3,4-tetrahydroisoquinoline-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)-amide hydrochloride acid (racemic mixture) **compound #8**;

10 S-2-(2-Amino-3-(hydroxy-phenyl)-S-1,2,3,4-tetrahydroisoquinoline-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)-amide hydrochloride acid (slow isomer) **compound #8A**;

2-S-Amino- 3-(4-hydroxy-phenyl)-1-{3-(R-2-hydroxy-3-phenyl-propylamino)-methyl}-S-3,4-dihydro-1H-isoquinolin-2-yl}propan-1-one ditrifluoroacetic salt (fast isomer) **compound #9A** ;

2-(tyrosyl)-3S-(D-phenylalanamido methyl)-1,2,3,4-tetrahydro isoquinoline hydro chloride salt **compound #10A**;

2-(tyrosyl)-3S-phenylalanamido methyl)-1,2,3,4-tetrahydro isoquinoline hydro chloride salt **compound #11A**;

2-Tyrosyl-3S-tyrosamidomethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride salt **compound #12A**;

2-Tyrosyl-3-benzoxycarboxamidomethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride salt **compound #13A**;

25 trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt **compound #14**;

trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer)

30 **compound #14A**; trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **compound #14B**;

and pharmaceutically acceptable derivatives thereof.

The compounds of the present invention are more preferably
5 selected from the group consisting of:

2-R-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow
isomer) **Compound 1B**; 2-S-(2-Amino-3-(4-hydroxy-2,6-
10 dimethyl-phenyl)-propionyl)-7-hydroxy-1,2,3,4-tetrahydro-
isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-
propyl)amide trifluoroacetic salt (racemic mixture) **compound**
#2; 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-
propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic
15 acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic
salt (fast isomer) **compound #3A**; 2-(2-Guanidino-3-(4-
hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-
isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-
propyl)-amide ditrifluoroacetic salt (slow isomer) **compound**
20 **#3B**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast
isomer) of **compound # 4A**;

25 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow
isomer) **Compound #4B**;

and pharmaceutically acceptable derivatives thereof.

30

The compound of the present invention is most preferably

2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-
propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic
35 acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic

salt (fast isomer) **compound #3A**; and pharmaceutically acceptable derivatives thereof.

There is also provided a pharmaceutically acceptable
5 compositions comprising the analgesic compounds of the invention, for use in the treatment of pain.

In a further aspect of this invention, there is provided the use of an analgesic compound selected from the group
10 consisting of:

(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (racemic mixture)
compound #5;

15 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (fast isomer)
compound #5A;

2- (2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
20 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (3-phenyl-
propyl)amide trifluoroacetic salt **compound #5B**;

2- (2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (racemic mixture)
25 **compound #6**;

2- (2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (fast isomer)
compound #6A;

30 2- (2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (slow isomer)
compound #6B;

2- (2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
35 1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-

fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (racemic mixture) **compound #7**;

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (fast isomer) **compound #7A**;

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (slow isomer) **compound #7B**;

and pharmaceutically acceptable derivatives thereof;
for the manufacture of peripheral analgesic for the treatment of pain.

15

In a preferred embodiment, there is provided the use of an analgesic compound selected from the group consisting of:

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) **compound #5A**; and

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt **compound #5B**;

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (fast isomer) **compound #7A**;

and pharmaceutically acceptable derivatives thereof;
for the manufacture of peripheral analgesic for the treatment of pain.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such

ester, of compound (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) compound (I) or an active metabolite or residue thereof.

5

It will be appreciated by those skilled in the art that the compounds of formula (I), depending of the substituents, may contain one or more chiral centres and thus exist in the form of many different isomers, optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. All such isomers, enantiomers and mixtures thereof including racemic mixtures are included within the scope of the invention

As used in this application, the term "alkyl" represents a substituted (by a halogen, hydroxyl, amino, or C₆₋₂₀ aryl) or unsubstituted, straight chain, branched chain, or cyclic hydrocarbon moiety, wherein said straight chain, branched chain, or cyclic hydrocarbon moiety can be interrupted by one or more heteroatoms (such as oxygen, nitrogen or sulfur).

20

The term "alkoxy" represents a substituted or unsubstituted alkyl group wherein the alkyl group is covalently bonded to an adjacent element through an oxygen atom (e.g., methoxy and ethoxy).

25

The term "alkoxyalkyl" represents an alkoxy group attached to the adjacent group by an alkyl group (e.g., methoxymethyl).

The term "aryl" represents a carbocyclic moiety which may be substituted or interrupted by at least one heteroatom (e.g., N, O, or S) and containing at least one benzenoid-type ring (e.g., phenyl and naphthyl).

The term "aralkyl" represents an aryl attached by the adjacent atom by an alkyl, (e.g. benzyl).

35

The term "acyl" refers to a radical derived from a carboxylic acid, substituted (by a halogen (F, Cl, Br, I), C₆₋₂₀ aryl or C₁₋₆ alkyl) or unsubstituted, by replacement of the -OH group.
5 Like the acid to which it is related, an acyl radical may be aliphatic or aromatic, substituted (by a halogen, C₁₋₅ alkoxyalkyl, nitro or O₂) or unsubstituted, and whatever the structure of the rest of the molecule may be, the properties of the functional group remain essentially the same (e.g.,
10 acetyl, propionyl, isobutanoyl, pivaloyl, hexanoyl, trifluoroacetyl, chloroacetyl, and cyclohexanoyl).

By the term "cyclic moiety" is meant" an C₃₋₁₂ cycloalkyl interrupted by at least one heteroatom such as O, N, or S.
15 Examples of cyclic moiety include but are not limited to piperazine, morpholine, and thiomorpholine.

The terms "amino protecting groups and oxygen protecting groups" are well known in the field of peptide synthesis .
20 Such amino protecting groups and oxygen protecting groups may be found in T.W Greene, Protective Groups In Organic Synthesis, (John Wiley & Sons, 2^o edition 1991). The appropriate protecting group for a particular synthetic scheme will depend on many factors, including the presence of
25 other reactive functional groups and the reaction conditions desired for removal as well known by persons skilled in the art of peptide chemistry.

The term "ED₅₀" as shown in table 1 for the PBQ writhing
30 assays is defined as the dose of drug which induces a 50% reduction in the number of writhes observed compared to the control. The term "ED₅₀" used in the hot-plate assays is defined as the dose of drug required to increase the latency

of response 2-fold compared to controls and was determined by parallel-line probit analysis.

The term " K_i " is the binding inhibition constant.

Unless indicated otherwise, the amino acid present in the analgesic compounds of the present invention are in the natural L-configuration.

Throughout the application, the isomers are usually identified as slow and fast isomers depending of their retention time when analyzed by HPLC (high pressure liquid chromatography). This characterization method is well accepted in the art of peptide chemistry, see for example US patent 4,599,325 issued on July 8, 1986.

The term "residue" when applied to an amino acid, means a radical derived from the corresponding amino acid by removing the hydroxyl of the carboxyl group and one hydrogen from the amino group.

A number of compounds based on the general formula (I), have been prepared and evaluated as opioid receptor ligands and systemically acting analgesic agents. These compounds are listed in **Table 1** along with their respective binding inhibition constants.

The present invention also provides for pharmaceutical compositions. Suitable compositions have a pharmaceutically effective amount of the compound of this invention, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier or adjuvant.

The present invention also provides for a method of treatment of pain in animals, such as mammals, including humans. The method comprises the steps of administering a

pharmaceutically effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, to the patient. A pharmaceutical composition as described above may also be used.

The following examples are used to better describe the invention. These examples are for the purpose of illustration only, and are not intended to limit the invention in any manner.

The opioid activity of the peptides was assessed *in vitro* using the guinea pig ileum (GPI) longitudinal muscle preparation and their antinociceptive activity was determined *in vivo* in PBQ induced writhing models (peripheral activity) and in the hot-plate test (central activity) in rodents. Antagonism of antinociception by the peripheral opioid antagonist N-methylnalorphine and by comparison of the activities in the writhing and hot-plate tests demonstrated that the analgesic effects were predominantly mediated in the periphery. Peripheral analgesia is shown by a high potency in the writhing test coupled with a low potency in the hot-plate test.

PBQ (phenyl-p-benzoquinone) induced writhing in mice is an assessment of both central and peripheral analgesia. For experimental protocol see Sigmund *et al.*, Proc. Soc. Exp. Biol. Med., 95, p. 729 (1957) which is incorporated herein by reference. Central analgesia is determined by the inhibition of a hot-plate response in mice. For experimental protocol see G. Woolfe and A. Macdonald, J. Pharmacol. Exp. Ther., 80, p.300 (1944) which is incorporated herein by reference. Assays measuring opioid receptor binding affinities for μ and δ receptors as well as GPI and MVD assays are determined through experimental protocol set out in Schiller *et al.*, Biophys. Res. Commun., 85, p.1322 (1975) incorporated herein by reference.

EXAMPLE 1

Radioligand Binding Assay

5

A. Membrane Preparation

Male Sprague-Dawley rats weighing between 350-450g were sacrificed by inhalation of CO₂. The rats were decapitated and the brains minus cerebellum were removed and place in
10 ice-cold saline solution and then homogenized in ice-cold 50 mM Tris buffer pH 7.4 (10ml/brain). The membranes were centrifuged at 14000 rpm for 30 min. at 4°C. The pellets were re-suspended in approximately 6ml/brain of ice-cold Tris buffer 50mM pH 7.4 and stored at -78°C until ready for use.
15 Protein quantification of the brain homogenate was conducted according to protein assay kit purchased (Bio-Rad).

B. Radioligand Inhibition

(³H)- DAMGO and (³H) DAGLE were used as radioligands for the μ
20 and δ receptors, respectively. Radioligand 50 μ l, membranes 100 μ l and serially diluted test compound were incubated for 1 hr at 22°C. Non specific binding was determined using 500 fold excess of unlabeled ligand in the presence of tracer and membranes. Free ligand was separated from bound by
25 filtration through Whatman GF/B paper (presoaked in polyethylenimine 1% aqueous solution) and rinsing with ice-cold 50mM Tris pH 7.4 using a Brandel cell harvester. The filters were dried and radioactivity was counted in a 24 well microplate in the presence of 500 ml scintillant per well.
30 Radioactivity was measured using a Wallac 1450 Microbeta counter.

Ki's for the various compounds were determined from the IC₅₀ according to the Cheng and Prusoff equation. Results of the
35 binding assay are summarized in **table 1**.

The activity of the peptide compounds on μ receptors was determined using the Guinea Pig Ileum (GPI) assay (longitudinal muscle preparation) according to the procedures described in Schiller et al., Biophys. Res. Commun., 85, p.1322 (1975). Activity results are summarized in table 1.

C)Writhing Assay

The test was performed on CD #1 male mice weighing between 18 and 22g. The mice were weighed and marked. They were injected, by intra-peritoneal route, with 0.3ml/20g by weight with a solution of phenylquinone at 0.02%. The contortions which appeared during a 15 minute time period following the injection were counted. The phenylquinone was injected at time intervals of 5, 20 or 60 minutes after administration of the compound (or medium, or standard) by subcutaneous route.

The 0.02% phenylquinone solution was prepared in the following fashion. 20mg of phenylquinone was dissolved in 5ml ethanol 90% (sigma, reagent, alcohol). The dissolved phenylquinone was slowly added to 95ml of distilled water continuously shaken and preheated (not boiled). The phenylquinone solution was left 2 hours before use, and at all times, protected from light. A new solution was prepared every day for the test.

Results of the assays are summarized below in **table 1**.

TABLE 1

Compound#	Ki^μ (nM)	Ki^δ (nM)	Ki^κ (nM)	IC₅₀ (nM) GPI	ED₅₀ (mg/kg) PBQ writhing
#3	2.03 ± 0.37	0.56 ± 0.09	276.6 ± 13.6		
#3B	0.5		164.3 ± 17.5	7.3 (2)	
#3A	2.94 ± 0.73		952 ± 122		3.8
#4B	0.7 ± 0.27	0.1 ± 0.02	20.6 ± 0.5	13.8	16.6
#6A	0.11 ± 0.02	0.84 ± 0.08	49.6 ± 8.7	5.1 (1)	2.4

Example 2

In vitro stability of the compounds of the invention in rat whole blood (RWB) at 37°C and in kidney brush border protease (KBBP) at 37°C.

a) In vitro stability in RWB at 37°C

Procedure:

- The compound was initially dissolved in water or in 10% methyl sulfoxide (DMSO)/water to make a stock solution of 10 mg/ml.
- The stock solution was added to 15 ml of freshly harvested rat whole blood and incubated at 37°C.
- Blanks were prepared without spiking with compounds in rat whole blood.
- Aliquots were then taken at specific time intervals, centrifuged, and a fraction of the supernatant was extracted with acetonitrile or with a solution of acetonitrile and 10% acetic acid.
- The solvent(s) was(were) removed by evaporation. The resulting residue was analyzed by HPLC.
- The results are shown in **Table 2**

TABLE 2

In vitro stability of the compounds of the invention in rat whole blood (RWB) at 37°C

Compound #	% Extraction Efficiency	Metabolites in RWB	half life in RWB	Correlation Coefficient(r)
4B	66.7%±4.13 (n=4)	none detected	>319 min.	0.5580
4A	93.3%±0.87 (n=6)	none detected	>126 min.	0.6738
5B	88.0%±0.4 (n=5)	none detected	>20 h	0.1066
5A	97.4%±2.7 (n=5)	none detected	>24 h	0.0409

5

b) In vitro stability in KBBP at 37°C

Procedure:

10

- 1.0 mg of the compounds were dissolved in 1 ml PBS pH 7.4 and 500 UL of proteases(1.14 mg of protein/ml) were added.
- An initial aliquot was taken at time 0, and the reaction was immediately stopped by placing the sample in a bath of boiling water for 2 minutes (the other time intervals were 5, 15,30,60,120,1440 minutes).
- Blank samples without compounds were also prepared.
- The aliquoted samples were filtered on a micron 0.45 filter and the resulting sample were analyzed by HPLC.

15

20

- The results are shown in **table 3**

TABLE 3In vitro stability in KBBP at 37°C

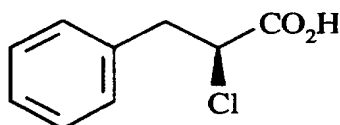
Compound #	Metabolites in KBBP	half life in KBBP	Correlation Coefficient(r)
4B	none detected	>24 h	0.0153
4A	1 detected after 24 h (6%)	>24 h	0.0486
5B	none detected	>24 h	0.0777
5A	none detected	>24 h	0.0017

EXAMPLE 3

Synthesis of 2-R-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic
5 acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt
compound #1

Step 1

10 Synthesis of S-2-Chloro-3-phenyl-propionic acid



Sodium nitrite (3.34 g, 48.41 mmol) in 15 ML of water
15 precooled at 0°C was added dropwise to S-phenylalanine (5 g,
30.27 mmol) suspended in 80 ML of 5 N hydrochloric acid
cooled with an ice / sodium chloride bath. After 5 h, the
bath was removed and the reaction was allowed to stand
overnight. While the mixture was stirred vigorously, solid
20 sodium carbonate (6.05 g) was added carefully in small
portions. The reaction mixture was extracted three times with
ether. The combined ether portion was dried and evaporated.
The residue was distilled at reduced pressure (5 mmHg) to
give the desired product as oil (3.63 g, 65%).

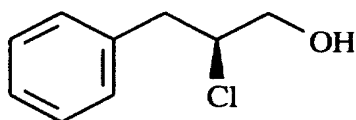
25

^1H NMR (CDCl_3) δ : 9-10 (br, 1 H), 7.31 (m, 5 H), 4.51 (dd, 1
H, $J=6.75$ Hz, $J=7.81$ Hz), 3.64 (dd, 1 H, $J=14.10$ Hz, $J=6.75$
Hz), 3.49 (dd, 1 H, $J=7.81$ Hz, $J=14.10$ Hz).

STEP 2

Synthesis of S-2-Chloro-3-phenyl-propan-1-ol

5



S-2-Chloro-3-phenyl-propionic acid (3.63 g, 19.66 mmol) in ether (10 ML) was added to lithium aluminum hydride (0.82 g, 21.63 mmol) in ether (20 ML) at 0°C. After 15 min., water (2 ML) was added. The precipitate was filtered off. The filtrate was evaporated. The residue was distilled under low pressure (5 mmHg) at 120°C to give the desired product as oil (2.13 g, 64%).

15

^1H NMR (CDCl_3) δ : 7.30 (m, 5 H), 4.23 (m, 1 H), 3.81 (m, 1 H), 3.71 (m, 1 H), 3.61 (dd, 1 H, $J=14.42$ Hz, $J=6.93$ Hz), 3.08 (1H, dd, $J=14.42$ Hz, $J=7.49$ Hz).

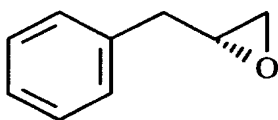
20 ^{13}C NMR (CDCl_3) δ : 136, 128, 127, 126, 65, 64, 40.

IR (NaCl film) ν_{max} : 3382, 2931, 1497, 1455, 1078, 1045 cm^{-1} .

STEP 3

Synthesis of R-2-Benzyl-oxirane

5



A solution of potassium hydroxide (4.45 g, 79.24 mmol) in water (10 ML) was added to S-2-chloro-3-phenyl-propan-1-ol
10 (1.93 g, 11.32 mmol) in CH₂Cl₂ (15 ML) at 0°C. The solution was stirred overnight at r.t. The organic phase was separated, dried over MgSO₄, filtered, and evaporated. The residue was distilled under reduced pressure (5 mmHg) at 85°C to yield the desired product as liquid (1.20 g, 79%).

15

¹H NMR (CDCl₃) δ: 7.30 (m, 5 H), 3.18(m, 1 H), 2.95(dd, 1 H), 2.84(dd, 1 H), 2.82(dd, 1 H), 2.57(dd, 1 H,).

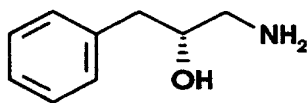
¹³C NMR (CDCl₃) δ: 134, 128, 127, 125, 52, 46, 38.

20

IR (NaCl film) ν_{max}: 3029, 1497, 1455, 847, 818 cm⁻¹.

STEP 4

25 Synthesis of R-1-Amino-3-Phenyl-Propan-2-ol



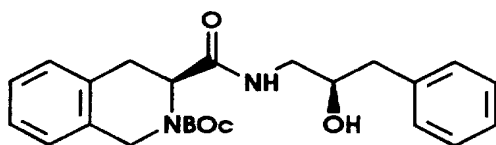
R-2-Benzyl-oxirane (5.02 g, 37.13 mmol) in aqueous ammonium hydroxide (25%) (80 mL) was stirred for 72 hr at room
30 temperature. Water was evaporated. The residue was distilled

under reduced pressure (5 mm Hg) at 140 °C to yield the desired product as white solid (3.24 g, 58%).

¹H NMR (CDCl₃) δ: 7.30 (m, 5 H), 3.73 (m, 1 H), 2.78 (m, 3 H),
s 2.56 (dd, 1 H).

Step 5

Synthesis of S-3-(R-2-Hydroxy-3-phenyl-propylcarbamoyl)-
5 3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl
ester



10

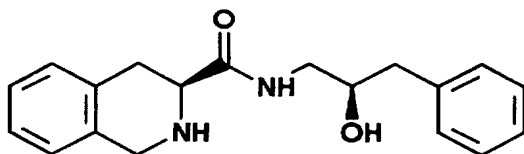
S-3,4-Dihydro-1H-isoquinoline-2,3-dicarboxylic acid 2-tert-butyl ester (0.50 g, 1.8 mmol) in dichloromethane (10 mL) was cooled to 0°C (N₂ atmosphere), and triethylamine (0.18 g, 0.73 mmol) was added, then isobutyl chloroformate (0.25 g, 1.8 mmol) was added. The reaction mixture was stirred for 1
15 hr. R-1-Amino-3-phenyl-propan-2-ol (0.27 g, 1.8 mmol) was added. The reaction mixture was warmed to room temperature and stirred for another 1 hr. The mixture was diluted with dichloromethane, washed with 10% KHSO₄ aqueous solution,
20 saturated NaHCO₃ aqueous solution and brine, then dried over MgSO₄, filtered, and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluant to provide the desired product as white solid (0.59 g, 80%).

25 ¹H NMR (CDCl₃) δ: 7.2 (m, 9H), 4.8-4.5 (br, 2H), 4.0 (br, 1H), 3.80 (br, 1H), 3.1 (br, 4H), 2.5 (br, 2H), 1.4-1.3 (2 s, 9H).

LRMS: m/z MH⁺ 411.4, (C₂₄H₃₁N₂O₄)⁺ requires 411.5.

Step 6

Synthesis of S-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic
5 acid (R-2-hydroxy-3-phenyl-propyl) amide



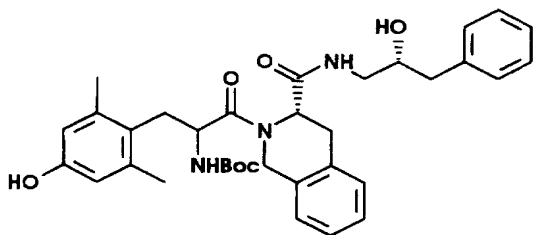
10 S-3-(R-2-Hydroxy-3-phenyl-propylcarbamoyl)-3,4-dihydro-1H-
isoquinoline-2-carboxylic acid tert-butyl ester (0.55 g, 1.28
mmol) was dissolved in TFA/CH₂Cl₂ (1:1) (5 mL). The solution
was stirred at room temperature for 1 hr. The solvent was
15 evaporated. The residue was dissolved in ethyl acetate,
washed with sat. NaHCO₃ aqueous solution and brine, dried
with Na₂SO₄, and evaporated to yield the desired product as
white solid (0.325 g, 83%)

20 ¹H NMR (acetone) δ: 7.9 (br, 1 H), 7.25-7.08 (m, 9 H), 4.09
(d, 1 H), 4.04 (d, 1 H, J=16.3 Hz), 3.93 (m, 1 H), 3.66 (dd,
1 H, J=4.8 Hz, J=10.26 Hz), 3.37 (m 1 H), 3.27 (m 1 H), 3.15
(m, 1 H), 2.89 (dd, 1 H, J=10.5 Hz, J=16.2 Hz), 2.75 (m, 2
H) ..

25

Step 7

Synthesis of {2-(4-Hydroxy-2,6-dimethyl-phenyl)-1-S-[3-R-(2-
5 hydroxy-3-phenyl-propylcarbamoyl)-3,4-dihydro-1H-
isoquinoline-2-carbonyl]-ethyl}-carbamic acid tert-butyl
ester



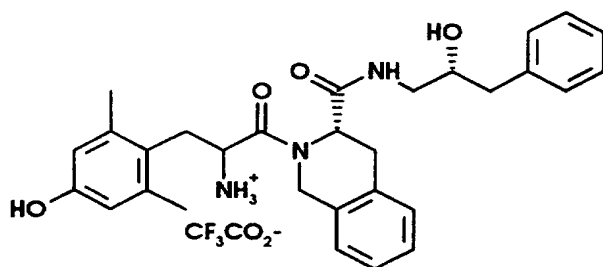
10

To a solution of 2-tert-butoxycarbonylamino-3-(4-hydroxy-2,6-
dimethyl-phenyl)-propionic acid (0.54 g, 1.75 mmol), S-
1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid[R-2-
15 hydroxy-3-phenyl-propyl]-amide (0.62 g, 1.75 mmol) and
HOBT.H₂O (0.29 g, 1.93 mmol) in DMF (5 mL) was added EDCI
(0.37 g, 1.93 mmol) under nitrogen at 0°C. After stirring
overnight at room temperature, the reaction mixture was
diluted with ethyl acetate, washed with 10% KHSO₄ aqueous
20 solution, saturated NaHCO₃ aqueous solution, and brine, then
dried over MgSO₄, filtered, and concentrated. The residue was
chromatographed on silica gel using ethyl
acetate/dichloromethane (1:1) as eluant to provide the fast
fraction as the desired product (0.40 g, 38%) and the slow
25 fraction as its isomer (0.40 g, 38%).

¹H NMR (acetone) (partial) δ: 8.1 (s, 1 H), 7.63 (br, 1H),
6.46 (2 H), 2.18 (s, 6 H), 1.39 (s, 9 H).

Step 8

Synthesis of 2-R-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) **compound #1A**



{2-(4-Hydroxy-2,6-dimethyl-phenyl)-1-S-[3-R-(2-hydroxy-3-phenyl-propylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carbonyl]-ethyl}-carbamic acid tert-butyl ester (0.40 g, 0.66 mmol) was dissolved in TFA/CH₂Cl₂ (1:1) (5 mL). The solution was stirred at room temperature for 1 hr. The solvent was evaporated. The residue was purified by HPLC under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.29 g, 71%).

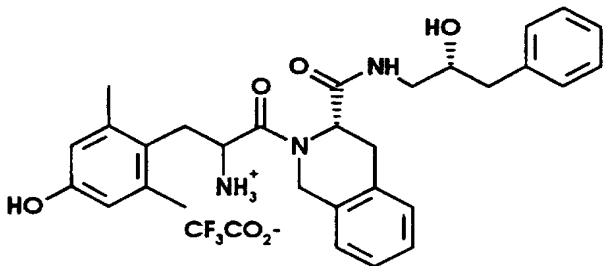
¹H NMR (methanol) δ : 7.87 (t, 1 H), 7.2-7.1 (m, 9 H), 6.79 (d, 1 H, J=7.2 Hz), 6.37 (s, 2 H), 4.93 (t, 1 H, J=5.0 Hz), 4.67 (dd, 1 H, J=11.8 Hz, J=4.2 Hz), 4.47 (d, 1 H, J=14.5 Hz), 3.74 (m, 1 H), 3.67 (s, 1 H), 3.37 (d, 1 H, J=14.5 Hz), 3.26 (d, 1 H, J=11.9 Hz), 3.15 (m, 4 H), 2.83 (dd, 1 H, J=5.7 Hz), 2.50 (m, 2 H), 2.30 (s, 6 H).

LRMS: m/z MH⁺ 502.6, [C₃₀H₃₆N₃O₄]⁺ requires 502.6

HPLC, purity 94%, rt=20.84

Step 9

Synthesis of 2-R-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **Compound 1B**



{2-(4-Hydroxy-2,6-dimethyl-phenyl)-1-S-[3-R-(2-hydroxy-3-phenyl-propylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carbonyl]-ethyl}-carbamic acid tert-butyl ester (0.40 g, 0.66 mmol) was dissolved in TFA/CH₂Cl₂ (1:1) (5 mL). The solution was stirred at room temperature for 1 hr. The solvent was evaporated. The residue was purified by HPLC under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.30 g, 73%).

20

¹H NMR (methanol) δ : 7.68 (t, 1 H), 7.30-7.00 (m, 9 H), 6.88 (d, 1 H), 6.60 (s, 1 H), 6.42 (s, 2 H), 5.02 (t, $\frac{1}{2}$ H), 4.72 (d, 1 H, J=12.7 Hz), 4.40 (d, $\frac{1}{2}$ H), 4.23 (dd, 1 H, J=11.9 Hz, J=4.0 Hz), 3.80 (d, $\frac{1}{2}$ H), 3.70 (m, 1 H), 3.25 (m, 1 H), 3.15 (m, 3 H), 2.82 (dd, 1 H, J=4.4 Hz, J=15.81 Hz), 2.5-2.3 (m, 2 H).

25

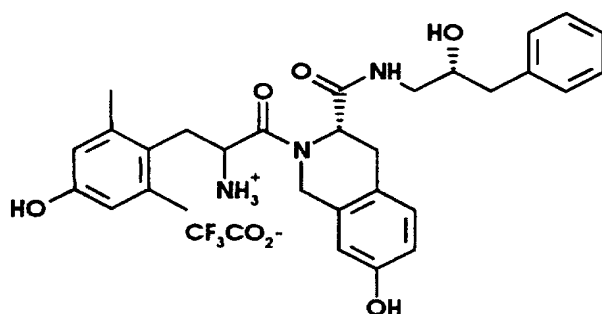
LRMS: m/z MH⁺ 502.6, [C₃₀H₃₆N₃O₄]⁺ requires 502.6

HPLC, purity 96%, rt=22.18

30

The following compounds were synthesized as generally described in example 3 except that the appropriate substitutions were made.

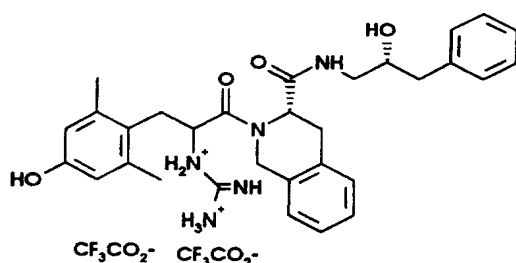
a) 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-7-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture) **compound #2**



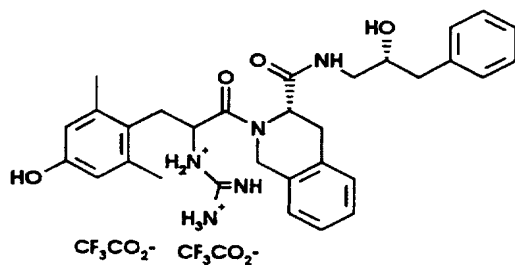
The residue was purified by HPLC under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.125 g, 74%).

HPLC purity 97%

b) 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt (racemic mixture) **compound #3**



- c) 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-
propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic
5 acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic
salt **compound #3A**



- 10 The residue was purified by HPLC under gradient condition
[0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V)
TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
followed by lyophilizing to yield the desire product as white
powder (0.087 g, 87%).

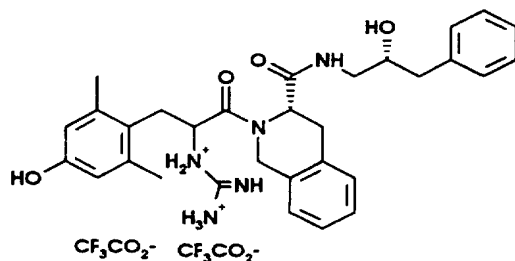
15

^1H NMR (methanol) δ : 7.91 (br, 1 H), 7.51 (d, 1 H, $J=8.4$ Hz),
7.25-7.00 (m, 9 H), 6.41 (s, 2 H), 5.02 (m, 1 H), 4.91 (m, 1
H), 4.70 (d, 1 H, $J=14.6$ Hz), 3.96 (d, 1 H, $J=14.6$ Hz), 3.76
(m, 1 H), 3.15 (m, 4 H), 3.05 (m, 2 H), 2.52 (m, 2 H).

20

HPLC purity 90%, $rt=19.18$

- d) 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-
propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic
25 acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic
salt **compound #3B**

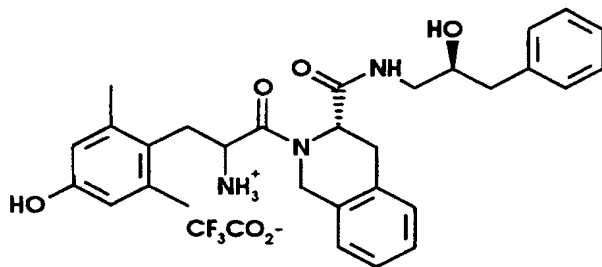


The residue was purified by HPLC under gradient condition
 5 [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.078 g, 78%).

10 ¹H NMR (methanol) δ : 7.88 (t, 1 H), 7.25-7.03 (m, 9 H), 6.47 (s, 2 H), 4.68 (d, 1 H, J=17.0 Hz), 4.49 (dd, 1 H, J=4.3 Hz, J=11.16 Hz), 4.40 (d, 1 H, J=17.0 Hz), 3.88 (t, 1 H, J=4.4 Hz), 3.64 (m, 1 H), 3.24 (m, 2 H), 3.12 (t, 2 H, J=5.8 Hz), 3.05 (dd, 1 H, J=4.3 Hz, J=13.8 Hz), 2.87 (dd, 1 H, J=3.7 Hz, J=16.3 Hz),
 15 2.30 (m, 2 H), 2.21 (s, 6 H).

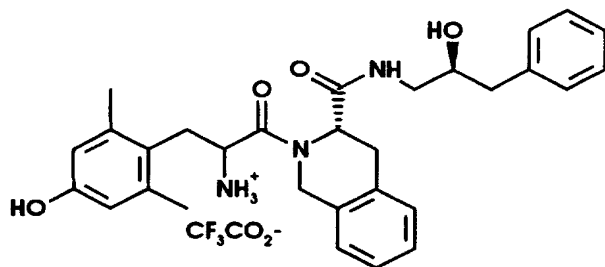
HPLC, purity 87%, rt=19.57

e) 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
 20 1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture) **compound #4**



f) 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) of **compound # 4A**

5



The residue was purified by HPLC under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
10 followed by lyophilizing to yield the desire product as white powder (0.040 g, 42%).

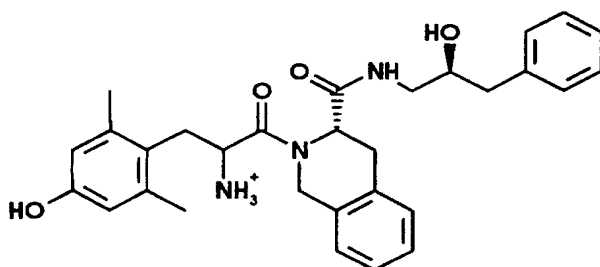
¹H NMR (methanol) δ : 7.87 (t, 1 H), 7.2-7.1 (m, 9 H), 6.79 (d, 1 H, J=7.2 Hz), 6.37 (s, 2 H), 4.93 (t, 1 H, J=5.0 Hz),
15 4.67 (dd, 1 H, J=11.8 Hz, J=4.2 Hz), 4.47 (d, 1 H, J=14.5 Hz), 3.74 (m, 1 H), 3.67 (s, 1 H), 3.37 (d, 1 H, J=14.5 Hz), 3.26 (d, 1 H, J=11.9 Hz), 3.15 (m, 4 H), 2.83 (dd, 1 H, J=5.7 Hz), 2.50 (m, 2 H), 2.30 (s, 6 H).

20 LRMS: m/z MH⁺ 502.6, [C₃₀H₃₆N₃O₄]⁺ requires 502.6

HPLC purity 99%, rt=22.0

g) 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **Compound #4B**

25



The residue was purified by HPLC under gradient condition
 5 [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.043 g, 55%).

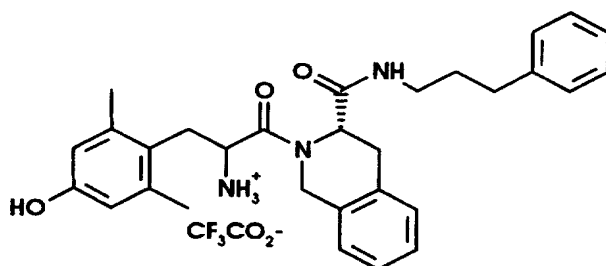
10 ¹H NMR (methanol) δ : 7.68 (t, 1 H), 7.30-7.00 (m, 9 H), 6.88 (d, 1 H), 6.60 (s, 1 H), 6.42 (s, 2 H), 5.02 (t, ½ H), 4.72 (d, 1 H, J=12.7 Hz), 4.40 (d, ½ H), 4.23 (dd, 1 H, J=11.9 Hz, J=4.0 Hz), 3.80 (d, ½ H), 3.70 (m, 1 H), 3.25 (m, 1 H), 3.15 (m, 3 H), 2.82 (dd, 1 H, J=4.4 Hz, J=15.81 Hz), 2.5-2.3 (m, 2
 15 H).

LRMS: m/z MH⁺ 502.6, [C₃₀H₃₆N₃O₄]⁺ requires 502.6

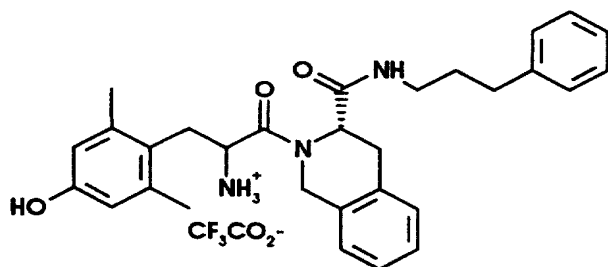
HPLC purity 96%, rt=23.58

20 h) 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture) **compound #5**

25



i) 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
 1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
 5 phenyl-propyl)amide trifluoroacetic salt (fast isomer)
compound #5A



10 The residue was purified by HPLC under gradient condition
 [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V)
 TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
 followed by lyophilizing to yield the desire product as white
 powder 0.074 g, 62%).

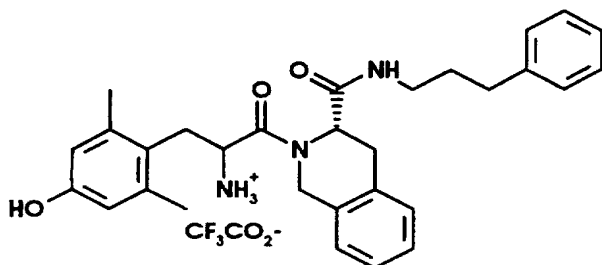
15

¹H NMR (methanol) δ : 7.94 (t, 1 H), 7.23-7.04 (m, 9 H), 6.79
 (d, 1 H, J=7.2 Hz), 6.37 (s, 2 H), 4.92 (t, 1 H, J=5.0 Hz),
 4.64 (dd, 1 H, J=11.8 Hz, J=4.3 Hz), 4.45 (d, 1 H, J=14.6
 Hz), 3.68 (d, 1 H, J=14.6 Hz), 3.26 (d, 1 H, J=12.0 Hz), 3.15
 20 (m, 4 H), 2.84 (dd, 1 H, J=15.55 Hz, J=5.6 Hz), 2.41 (t, 2 H,
 7.5 Hz), 2.29 (s, 6 H), 1.60 (m, 2 H).

LRMS: m/z MH⁺ 486.3, [C₃₀H₃₆N₃O₃]⁺ requires 486.6

25 HPLC purity 95%, rt=19.77

- j) 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (3-phenyl-
5 propyl)amide trifluoroacetic salt **compound #5B**



The residue was purified by HPLC under gradient condition
10 [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V)
TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
followed by lyophilizing to yield the desire product as white
powder (0.074 g, 75%).

15 ^1H NMR (methanol) δ : 7.78 (t, 1 H), 7.23-6.90 (m, 9 H), 6.47
(s, 2 H), 5.03 (t, $\frac{1}{2}$ H), 4.67 (d, 1 H, $J=16.9$ Hz), 4.66 (m, $\frac{1}{2}$
H), 4.45 (d, $\frac{1}{2}$ H), 4.21 (dd, 1 H, $J=4.0$ Hz, $J=11.9$ Hz), 3.80
(d, $\frac{1}{2}$ H), 3.72 (t, 1 H, $J=4.4$ Hz), 3.15 (m, 2 H), 2.83 (dd, 1
H, $J=16.04$ Hz, $J=3.6$ Hz), 2.25 (m, 1 H), 2.21 (s, 6 H), 2.11
20 (dd, 1 H, $J=16.05$ Hz, $J=5.2$ Hz), 1.53 (m, 2 H).

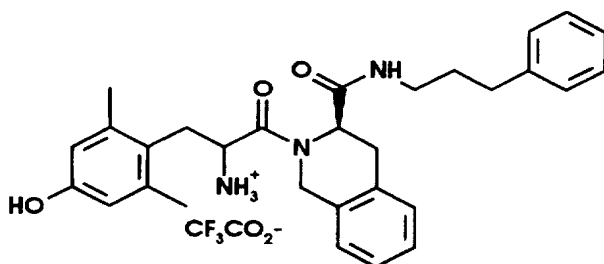
LRMS: m/z MH^+ 486.3, $[\text{C}_{30}\text{H}_{36}\text{N}_3\text{O}_3]^+$ requires 486.6

HPLC, purity 95%, $\text{rt}=20.4$

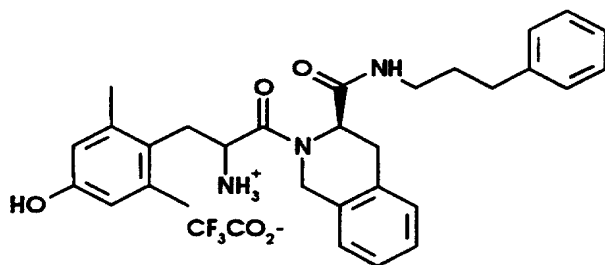
25

- k) 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (racemic mixture)
compound #6

30



- 1) 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
5 phenyl-propyl)amide trifluoroacetic salt (fast isomer)
compound #6A



- 10 The residue was purified by HPLC under gradient condition
[0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V)
TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
followed by lyophilizing to yield the desire product as white
powder 0.074 g, 62%).

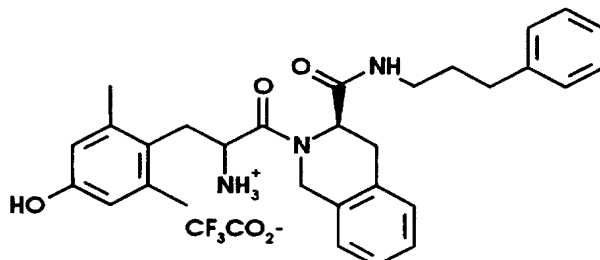
15

- ^1H NMR (methanol) δ : 7.94 (t, 1 H), 7.23-7.04 (m, 9 H), 6.79
(d, 1 H, $J=7.2$ Hz), 6.37 (s, 2 H), 4.92 (t, 1 H, $J=5.0$ Hz),
4.64 (dd, 1 H, $J=11.8$ Hz, $J=4.3$ Hz), 4.45 (d, 1 H, $J=14.6$
Hz), 3.68 (d, 1 H, $J=14.6$ Hz), 3.26 (d, 1 H, $J=12.0$ Hz), 3.15
20 (m, 4 H), 2.84 (dd, 1 H, $J=15.55$ Hz, $J=5.6$ Hz), 2.41 (t, 2 H,
7.5 Hz), 2.29 (s, 6 H), 1.60 (m, 2 H).

LRMS: m/z MH^+ 486.3, $[\text{C}_{30}\text{H}_{36}\text{N}_3\text{O}_3]^+$ requires 486.6

- 25 HPLC purity 98%, $\text{rt}=19.65$

m) 2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (slow isomer)



5 **compound #6B**

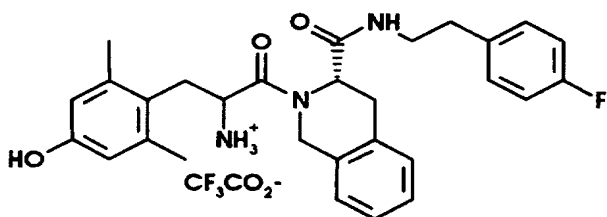
The residue was purified by HPLC under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
 10 followed by lyophilizing to yield the desire product as white powder (0.074 g, 75%).

¹H NMR (methanol) δ : 7.78 (t, 1 H), 7.23-6.90 (m, 9 H), 6.47 (s, 2 H), 5.03 (t, $\frac{1}{2}$ H), 4.67 (d, 1 H, J=16.9 Hz), 4.66 (m, $\frac{1}{2}$ H), 4.45 (d, $\frac{1}{2}$ H), 4.21 (dd, 1 H, J=4.0 Hz, J=11.9 Hz), 3.80 (d, $\frac{1}{2}$ H), 3.72 (t, 1 H, J=4.4 Hz), 3.15 (m, 2 H), 2.83 (dd, 1 H, J=16.04 Hz, J=3.6 Hz), 2.25 (m, 1 H), 2.21 (s, 6 H), 2.11 (dd, 1 H, J=16.05 Hz, J=5.2 Hz), 1.53 (m, 2 H).

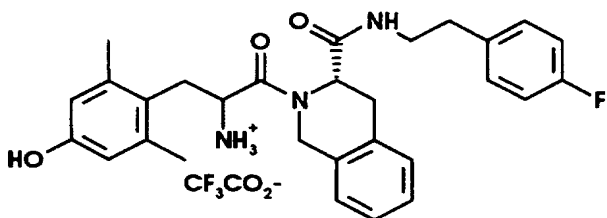
20 LRMS: m/z MH⁺ 486.3, [C₃₀H₃₆N₃O₃]⁺ requires 486.6

HPLC, purity 98%, rt=20.11

- n) 2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (racemic
5 mixture) **compound #7**



- o) 2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
10 1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt **compound
#7A**

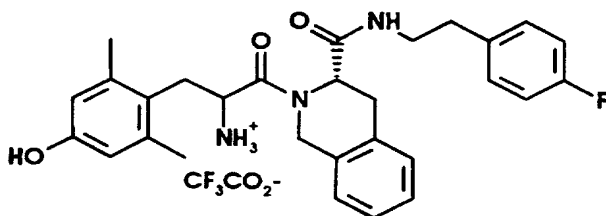


- 15 The residue was purified by HPLC under gradient condition
[0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V)
TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
followed by lyophilizing to yield the desire product as white
20 powder (0.106 g, 57%).

- ¹H NMR (methanol) δ : 7.98 (t, 1H), 7.17-6.77 (m, 8 H), 6.35
(s, 2 H), 4.92 (dd, 1H, J=4.1 Hz, J=5.6 Hz), 4.64 (dd, 1 H,
J=4.2 Hz, J=11.8 Hz), 4.40 (d, 1 H, J=14.6 Hz), 3.37 (d, 1 H,
25 J=14.6 Hz), 3.25 (m, 3 H), 3.14 (dd, 1 H, J=4.3 Hz, J=13.7
Hz), 3.05 (dd, 1 H, J=4.0 Hz, J=15.6 Hz), 2.78 (dd, 1 H,
J=5.8 Hz, J=15.6 Hz), 2.58 (t, 1 H, J=7.0 Hz), 2.28 (s, 6 H).

HPLC, purity 99%, rt=18.62.

- p) 2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt **compound**
#7B



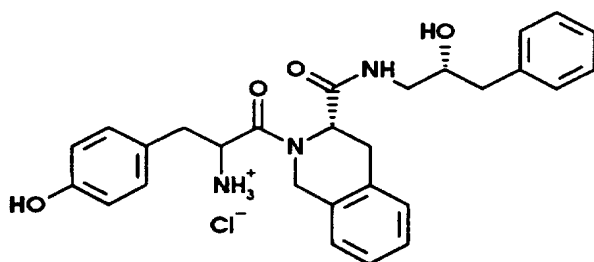
- 10 The residue was purified by HPLC under gradient condition
[0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V)
TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min],
followed by lyophilizing to yield the desire product as white
powder.

15

- ¹H NMR (methanol) δ : 7.84 (t, 1 H), 7.25-7.05 (m, 4 H), 6.98-
6.88 (m, 5 H), 6.61 (s, 1 H), 6.43 (s, 2 H), 5.05 (t, ½ H,
J=5.0 Hz), 4.70 (d, 1 H, J=17.0 Hz), 4.69 (m, ½ H), 4.44 (d,
½ H, J=15.0 Hz), 4.40 (d, 1 H, J=17.0 Hz), 4.19 (dd, 1 H,
20 J=4.0 Hz, J=11.97 Hz), 3.77 (d, 1 H, J=15.0 Hz), 3.68 (t, 1
H, J=4.5 Hz), 3.25 (m, 1 H), 3.15 (m, 1 H), 2.74 (dd, 1 H,
J=3.6 Hz, J=16.2 Hz), 2.55 (m, 2 H), 2.17 (s, 6 H), 2.04 (dd,
1 H, J=16.1 Hz, J=5.2 Hz).

25

- q) S-2-(2-Amino-3-(hydroxy-phenyl)-S-1,2,3,4-
tetrahydroisoquinoline-carboxylic acid (R-2-hydroxy-3-phenyl-
propyl)-amide hydrochloride acid (slow isomer) **compound #8A**



LRMS, m/z MH^+ 474.4, $[C_{28}H_{32}N_3O_4]^+$ 474.6

HPLC, purity 98%, $rt=45.69$

5

EXAMPLE 4

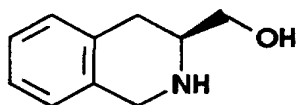
2-S-Amino- 3-(4-hydroxy-phenyl)-1-{3-(R-2-hydroxy-3-phenyl-
propylamino)-methyl}-S-3,4-dihydro-1H-isoquinolin-2-
yl}propan-1-one ditrifluoroacetic salt **compound #9A**

10

Step 1

Synthesis of S-(1,2,3,4-Tetrahydro-Isoquinoline-3-yl)-
Methanol

15



Borane-methyl sulfide complex (31.0 mmol) was added to the
gently refluxing solution of S-1,2,3,4-tetrahydro-3-
isoquinoline carboxylic acid (5.0 g, 28.22 mmol) and boron
trifluoride etherate (28.22 mmol) in THF (100 ML) under
nitrogen. The solution was then refluxed overnight. The
reaction mixture was cooled to 0 °C and quenched by slow
addition of methanol (5 ML). the solvent was evaporated and
the residue was dissolved in aqueous solution of sodium
hydroxide (6 M) and reflux for 2 hr. the mixture was filtered
through a cerite pad. The filtrate was extracted with
chloroform, washed with brine, dried over $MgSO_4$ and

20

25

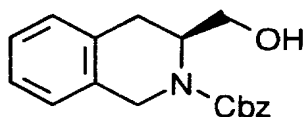
evaporated. The crude product was recrystallized from CHCl_3 to give the desired product as crystals (4.0 g, 87%).

^1H NMR (CDCl_3) δ : 7.10 (4 H, m), 4.06 (2 H, s), 3.77 (1 H, dd, $J=10.95$ Hz, $J=3.64$ Hz), 3.52 (1 H, dd, $J=10.95$ Hz, $J=7.80$ Hz), 3.08 (1 H, m), 2.70 (1H, dd, $J=16.27$ Hz, $J=4.26$ Hz), 2.59 (1H, dd, $J=16.27$ Hz, $J=10.85$ Hz).

^{13}C NMR (CDCl_3) δ : 128.43, 125.34, 125.14, 124.98, 64.81, 54.18, 46.97, 30.05.

Step 2

Synthesis of S-3-Hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl ester

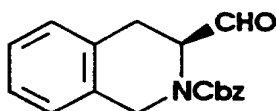


Benzylchloroformate (4.55 g, 26.69 mmol) was added to S-1,2,3,4-tetrahydroisoquinolin-3-yl)-methanol (3.96 g, 24.26 mmol) in water / dichloromethane (1:1, 100 ML). The solution was stirred vigorously for 3 h. The organic phase was washed with 10% aqueous KHSO_4 , 5% aqueous NaHCO_3 and brine, dried over MgSO_4 , filtered and evaporated. The residue was chromatographed using ethyl acetate:hexane (1:1) as eluant to yield the titled compound as oil (7.13 g, 99%).

^1H NMR (CDCl_3) δ : 7.38(5 H, m), 7.16(4 H, m), 5.21(2 H, dd), 4.80(1 H, dd), 4.77(1 H, br), 4.42(1 H, dd), 3.46-3.56(2 H, br), 3.06(1 H, dd, $J=15.98$ Hz, $J=5.88$ Hz), 2.69(1 H, dd, $J=16.0$ Hz, $J=5.88$ Hz), 2.66(1 H, br).

Step 3

Synthesis of S-3-Formyl-3,4-dihydro-1H-isoquinoline-2-
5 carboxylic acid benzyl ester

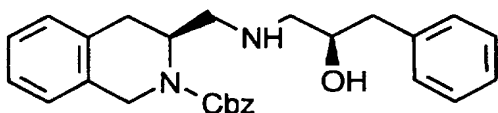


Periodinane (8.96g, 21.20 mmol) was added to S-3-
10 hydroxymethyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid
benzyl ester (5.73 g, 19.27 mmol) in dichloromethane (150
ML) at r.t. The mixture was stirred for 20 min. The
solution was washed with a mixture of 5% NaHCO₃ and 5%
Na₂S₂O₄ aqueous solution, brine, dried over MgSO₄, and
15 evaporated. The residue was purified by chromatography
using ethyl acetate / hexane (1:1) as eluant to yield the
desired product as oil (4.15 g, 73%).

¹H NMR (CDCl₃) δ : 9.54-9.48 (2 s, 1 H), 7.46-7.09 (m, 9 H),
20 5.27 (s, 1 H), 5.21 (s, 1 H), 4.94 (dd, $\frac{1}{2}$ H, J=6.4 Hz,
J=3.5 Hz), 4.80 (d, 1 H, J=16.4 Hz), 4.72 (t, $\frac{1}{2}$ H, J=4.7
Hz), 4.65 (d, 1 H, J=16.5 Hz), 3.28 (dd, 1 H, J=6.0 Hz,
J=13.3 Hz), 3.10 (m 2 H).

Step 4

Synthesis of S-3-[(R-2-Hydroxy-3-phenyl-propylamino)-
methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl
ester



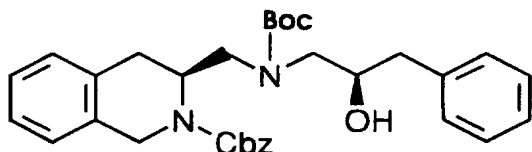
The mixture of S- 3-formyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl ester (1.18 g, 3.99 mmol), R-1-amino-3-phenyl-propan-2-ol (0.60 g, 3.99 mmol), NaOAc (0.65 g, 7.98 mmol) and 4-Å molecular sieves (1.0 g) in methanol (20 ML) was stirred at r.t. for 3 h. NaBH₃CN (0.38 g, 5.99 mmol) was added. The mixture was stirred for another 3 h. 10% KHSO₄ aqueous solution was added to PH=4. The mixture was basified with saturated NaHCO₃ and most of the methanol was removed under reduced pressure. The mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over MgSO₄, filtered and concentrated. The residue was chromatographed using ethyl acetate as eluant to yield the titled compound as white solid (0.80 g, 46%)

15

¹H NMR (CDCl₃) δ: 7.14-7.41 (m, 14 H), 5.24-5.16 (dd, 2 H), 4.87 (br, 1 H), 4.55 (br, 1H), 4.33 (br, 1H), 3.80 (br, 1H), 3.10 (br, 1H), 2.70 (m, 4 H), 2.40 (m, 3 H).

Step 5

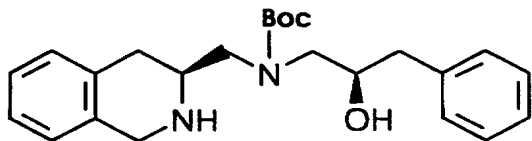
Synthesis of S-3-([tert-Butoxycarbonyl-(2-R-hydroxy-2-phenyl-propyl)-amino]-methyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl ester



(Boc)₂O (0.44 g, 2.0 mmol) was added to a mixture of triethylamine (0.19 g, 1.83 mmol) and S-3-[(R-2-hydroxy-3-phenyl-propylamino)-methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl ester (0.79 g, 1.83 mmol) in DMF (5 ML). The reaction mixture was stirred at r.t. for 2 hr. The mixture was poured into water, extracted with ethyl acetate. The organic phase was washed with 10% KHSO₄ aqueous solution and brine, dried, and evaporated. The residue was purified by chromatography using ethyl acetate / hexane (3 : 7) as eluant to yield the desired product as oil (0.83 g, 85%).

Step 6

Synthesis of S-(R-2-Hydroxy-3-phenyl-propyl)-(1,2,3,4-tetrahydro-isoquinolin-3-ylmethyl)-carbamic tert-butyl ester



A solution of S-3-([tert-butoxy carbonyl-(R-2-hydroxy-3-phenyl-propyl)-amino)-methyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzyl ester (0.066 g, 0.14 mmol) in

methanol (10 ML) containing HOAc (0.1 ML) was added 10% Pd-C (0.015 g) catalyst. The mixture was stirred under hydrogen for 1 hr. The catalyst was filtered off. The filtrate was evaporated. The residue was portioned between
5 saturated NaHCO₃ aqueous solution and ethyl acetate. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated to yield the desired produce as white solid. (0.039 g, 71%)

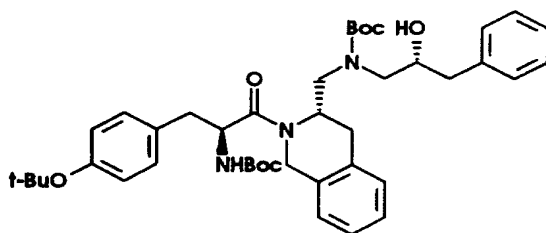
10 ¹H NMR (HOAc salt form) (acetone) δ: 7.99 (br, 2 H), 7.28-7.07 (m, 9 H), 4.15 (m, Br, 3 H), 3.85 (m, 2 H), 3.45 (br, 1 H), 3.25 (br, 1H), 2.95 (br, 1H), 2.75 (br, 4H).

LRMS, m/z MH⁺ 397.2, [C₂₄H₃₃N₂O₃]⁺ requires 397.5

15

Step 7

Synthesis of S-[1-(3-[[tert-Butoxycarbonyl-(R-2-hydroxy-3-phenyl-propyl)-amino]-methyl]-3,4-dihydro-1H-isoquinoline-2-S-carbonyl)-2-(4-tert-butoxy-phenyl)-ethyl]-carbamic acid
20 tert-butyl ester

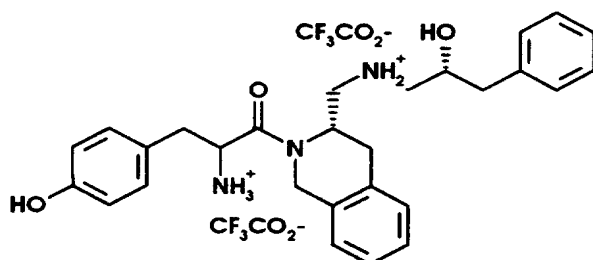


25 N-t-Boc-O-t-butyl-S-tyrosine (0.1 g, 0.26 mmol) in THF (5 mL) was cooled to 0°C (N₂ atmosphere), and triethylamine (0.026 g, 0.26 mmol) was added, then isobutyl chloroformate (0.036 g, 0.26 mmol) was added. The reaction mixture was stirred for 1 hr. S-(R-2-Hydroxy-3-phenyl-propyl)-(1,2,3,4-tetrahydro-isoquinolin-3-ylmethyl)-carbamic tert-butyl ester
30

(0.1 g, 0.26 mmol) was added. The reaction mixture was warmed to room temperature and stirred for another 1 hr. The mixture was diluted with dichloromethane, washed with 10% aqueous KHSO_4 , saturated aqueous NaHCO_3 , and brine, then dried over MgSO_4 , filtered, and concentrated. The residue was chromatographed on silica gel using ethyl acetate as eluant to provide the desired product as white solid (0.14 g, 70%).

10 Step 8

Synthesis of 2-S-Amino- 3-(4-hydroxy-phenyl)-1-{3-(R-2-hydroxy-3-phenyl-propylamino)-methyl}-S-3,4-dihydro-1H-isoquinolin-2-yl}propan-1-one ditrifluoroacetic salt (fast isomer) **compound #9A**



S-[1-(3-([tert-Butoxycarbonyl-(R-2-hydroxy-3-phenyl-propyl)-amino]-methyl)-3,4-dihydro-1H-isoquinoline-2-S-carbonyl)-2-(4-tert-butoxy-phenyl)-ethyl]-carbamic acid tert-butyl ester (0.14 g, 0.23 mmol) was dissolved in 4N HCl in dioxane (5 ML). The solution was stirred at room temperature for 0.5 hr. The solvent was evaporated. The residue was dissolved in ethyl acetate, washed with water. The aqueous phase was dried by lyophilizing. The residue was purified by HPLC under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 ML/min], followed by lyophilizing to yield the desire product as white powder (0.070 g, 58%).

LRMS, m/z MH^+ 460.1, $[C_{28}H_{33}N_3O_3]^+$ 460.6

HPLC, Purity 98%, $rt=39.12$

5

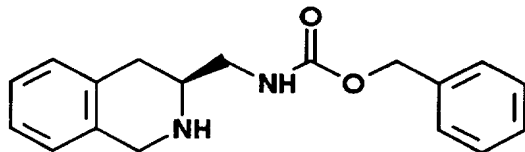
EXAMPLE 5

Synthesis of 2-(tyrosyl)-3S-(D-phenylalanyl)-
10 1,2,3,4-tetrahydro isoquinoline hydro chloride salt **compound**
#10A

Step 1

15

Synthesis of 3S-benzoyl carboxamidomethyl-1,2,3,4-tetrahydro
isoquinoline



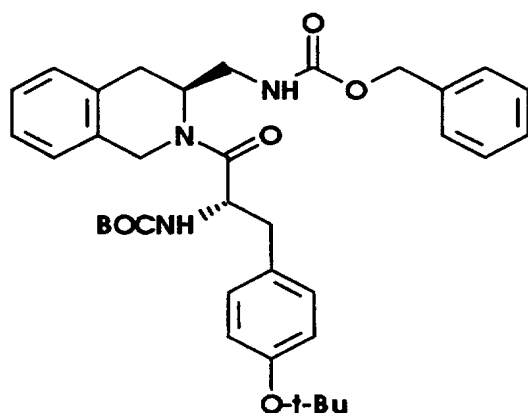
20

Diamine (87 mg, 0.54 mmol) in methylene chloride (5 ml) was
treated with 4-dimethyl amino pyridine (2 mg) and
carbobenzoxy imidazole (109 mg, 0.54 mmol). The mixture was
stirred five days. The crude product was purified on
25 preparative TLC to give desired product (120 mg).

1H NMR (400 MHz, $CDCl_3$), δ : 2.55 (dd, $J_1 = 13.8$ Hz, $J_2 = 10.4$
Hz, 1H), 2.78 (dd, $J_1 = 13.8$ Hz, $J_2 = 3.0$ Hz, 1H), 3.04 (m,
1H), 3.15 (m, 1H), 3.49 (m, 1H), 4.02 (s, 2H), 5.14 (s, 2H),
30 5.69 (s, 1H), 7.01-7.37 (m, 9H).

Step 2

Synthesis of 1S-t-butoxy carboxamido-2-(4-t-butoxy-phenyl)-
 (3-benzoxycarboxamido methyl-3,4-dihydro-1H-isoquinoline-2-
 5 yl)-ketone



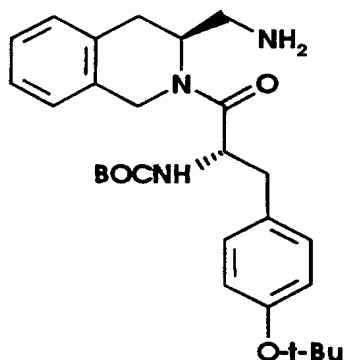
To an ice-cold DMF solution (4 ml) of mono-CBZ-protected
 diamine (94 mg, 0.34 mmol), Boc-Tyr-(t-Bu)-OH and 1-
 10 hydroxybenzotriazole (48.4 mg, 0.358 mmol) was added 1,1'-
 cyclohexyl carbodimide (DCC, 73.8 mg, 0.358 mmol). The
 resulting mixture was stirred for 36 hours as it warmed to
 room temperature. Solvent was evaporated and the crude
 product was purified on silica gel (hexane:EtOAc = 2:1) to
 15 give desired product (60 mg).

^1H NMR (400 MHz, CDCl_3), δ : 1.24-1.37 (ms, 18H), 1.96 (dd, J_1
 = 14.8 Hz, J_2 = 5.2 Hz, 1H), 2.35 and 2.70 (2d, J_A = 14.8 Hz,
 J_{B1} = 14.8 Hz, J_{B2} = 1.7 Hz, 1H), 2.90-3.07 (m, 3H), 3.39 (m,
 1H), 3.99 and 4.70 (2d, J = 16.5 Hz, 1H), 4.25 (m, 1H), 4.94-
 20 5.10 and 5.20 (m, 3H), 5.45 and 5.46 (2d, J = 8.6 Hz, 1H),
 6.01 (m, 1H), 6.71 and 6.90 (2d, J = 8.5 Hz, 2H), 7.06 (d, J
 = 8.5 Hz, 2H), 7.08-7.34 (m, 9H).

Step 3

Synthesis of 2-(N-Boc-(O-t-bu))-tyrosyl-3S-aminomethyl-1,2,3,4-tetrahydro isoquinoline

5



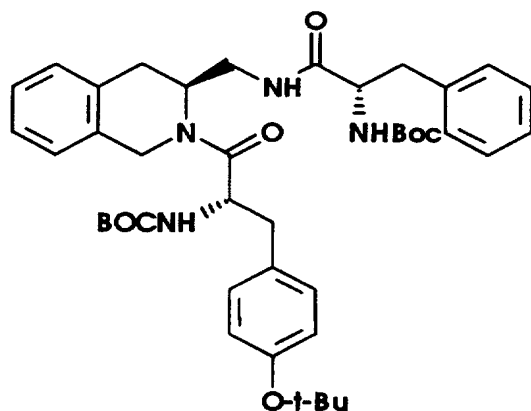
A methanolic solution of of 1S-t-butoxy carboxamido-2-(4-t-butoxy-phenyl)-(3-benzoxycarboxamidomethyl-3,4-dihydro-1H-isoquinoline-2-yl)-ketone (190 mg, 0.325 mmol) was
10 hydrogenated for three hours under the catalysis of Pd/C (10%, 34.5 mg). It was filtered and the filtrate was evaporated to give a solid which was treated with NaOH (0.1 N) and extracted with CHCl₃. The organic layer was
15 evaporated to dryness to give desired product (112 mg).

¹H NMR (400 MHz, CDCl₃), δ: 1.21, 1.26, 1.36, 1.39 (ms, 6xCH₃), 2.05 (dd, J₁ = 19 Hz, J₂ = 7Hz, 1H), 2.44 (d, J = 19.0 Hz, 1H), 2.53 (m, 1H), 2.75, 2.85-3.00 (m, 4H), 3.73, 4.15, 20 4.65, 4.95 (4d, J = 20 Hz, 2H), 3.97 (m, 1H), 4.76-5.06 (m, 2H), 4.44, 4.48 (2d, J = 11.0 Hz, 1H), 6.68-7.20 (m, 8H).

Step 4

25

Synthesis of 2-(N-Boc-(O-t-bu)-tyrosyl)-3-(N-Boc-D-phenylalanamidomethyl)-1,2,3,4-tetrahydroisoquinoline



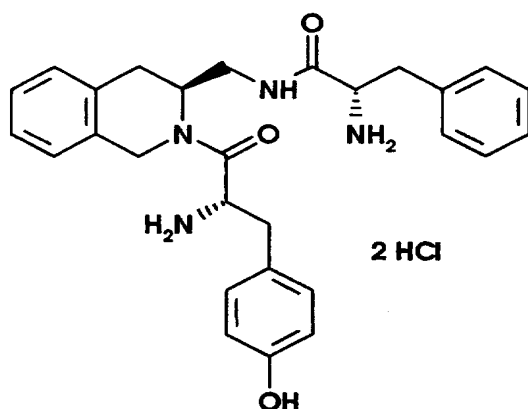
The free amine 2-(N-Boc-(O-t-bu))-tyrosyl-3S-aminomethyl-1,2,3,4-tetrahydro isoquinoline (56 mg, 0.117 mmol) was coupled to Boc-D-Phe (35.5 mg, 0.13 mmol) activated by
 5 isopropyl chloroformate (1.0 M solution, 0.135 ml, 0.135 mmol). After chromatography, the desired product was obtained (72 mg).

¹H NMR (400 MHz, CDCl₃), δ: 1.29, 1.34, 1.36, 1.40, 1.41,
 10 1.43 (ms, 27H), 2.07 (dd, J₁ = 17.1 Hz, J₂ = 4.8 Hz, 1H),
 2.41 (d, J = 17.1 Hz, 1H), 2.64 (btr, J = 15.2 Hz, 1H), 2.86-
 3.21 (m, 4H), 3.96, 4.64 (2d, J = 14.3 Hz, 1H), 4.25, 5.02
 (2d, J = 18.6 Hz, 2H), 4.03-5.15 (m, 5H), 5.24 (d, J = 5.7
 Hz, 1H), 5.39, 5.48 (2d, J = 8Hz, 1H), 6.84-7.32 (m, 13H).

15

Step 5

Synthesis of 2-(tyrosyl)-3S-(D-phenylalanamido methyl)-
 20 1,2,3,4-tetrahydro isoquinoline hydro chloride salt **compound**
5A



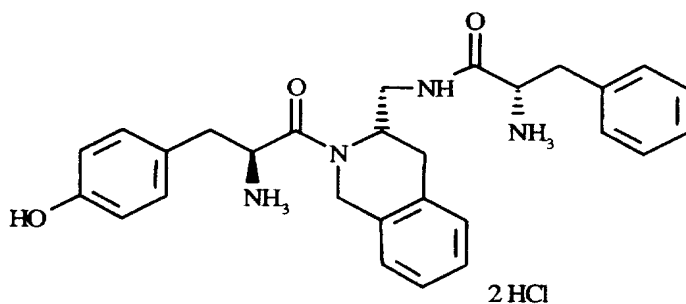
2-(N-Boc-(O-t-bu)-tyrosyl)-3-(N-Boc-D-phenylalanamidomethyl)-
1,2,3,4-tetrahydroisoquinoline was deprotected by usual
5 methods to yield the titled compound as the hydrochloride
salt (22 mg).

¹H NMR (400 MHz, MeOH-d₄), δ : 1.18 (dd, $J_1 = 14.9$ Hz, 4.0
Hz), 2.54 (d, $J = 14.9$ Hz), 2.65 (dd, $J_1 = 15$ Hz, $J_2 = 3.0$ Hz),
10 2.81 (m) (all four sets of peaks, 2H), 3.00-3.25 (m, 4H),
3.92 (d, $J = 14.9$ Hz), 4.00 (m) 4.06 (tr, $J = 8.9$ Hz), 4.16
(tr, $J = 8.9$ Hz), 4.43 (d, $J = 18.8$ Hz), 4.63 (d, $J = 18.8$
Hz), 4.67 (tr, $J = 7.9$ Hz), 4.74 (d, $J = 18.8$ Hz), 5.00 (m)
(all nine sets of peaks, 7H), 6.72 (d, $J = 8.9$ Hz), 6.90 (d,
15 $J = 8.9$ Hz), 7.09 (d, $J = 8.9$ Hz), 7.17 (d, $J = 8.9$ Hz),
7.03-7.70 (m) (all five sets of peaks, 13 H), 8.04 (d, $J =$
7.9 Hz), 8.48 (m), 8.60 (m) (all three sets of peaks, 1H).

The following compounds were synthesized as generally
20 described in example 5, except that the appropriate
substitutions were made.

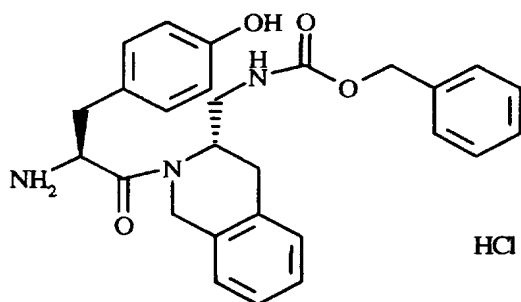
a) 2-(tyrosyl)-3S-phenylalanamido methyl)-1,2,3,4-tetrahydro
isoquinoline hydro chloride salt **compound #11A**

56



¹H NMR (400 MHz, MeOH-d₄), δ : 1.85 (d, J = 14.9 Hz, 1H),
 1.93 (dd, J_1 = 14.9Hz, J_2 = 5Hz, 1H), 2.52, 2.76 (2m, 2H),
 3.03-3.17 (m, 2H), 3.64 (m, 1H), 4.05 (m, 1H), 4.44 (d, J =
 18.8 Hz, 1H), 4.61 (d, J = 18.8 Hz, 1H), 5.04 (m, 1H), 6.78-
 7.50 (m, 13H), 7.60-8.03 (2d, J = 8.9 Hz, 1H), 8.27-8.47 (2m,
 1H).

b) 2-Tyrosyl-3-benzoxycarboxamidomethyl-1,2,3,4-
 tetrahydroisoquinoline hydrochloride salt **compound# 13A**



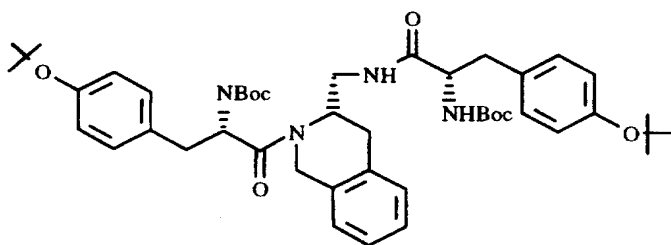
¹H NMR (400 MHz, MeOH-d₄), δ : 2.16 (dd, J_1 = 14.6 Hz, J_2 = 4.9
 Hz, 1H), 2.58 (dd, J_1 = 14.6 Hz, J_2 = 2 Hz, 1H), 2.62 (dd, J_1
 = 12 Hz, J_2 = 9.8 Hz, 1H), 2.90-3.15 (m, 2H), 3.75 (bs, 1H),
 4.44 (d, J = 17.6 Hz, 1H), 4.66 (d, J = 17.6 Hz, 1H), 4.30-
 4.76 (2d, J = 15.6 Hz, 1H), 5.05 (tr. J = 3.5 Hz, 1H), 5.10
 (d, J = 11.7 Hz, 1H), 5.23 (d, J = 11.7 Hz, 1H), 6.67-7.40
 (m, 13H).

EXAMPLE 6

Synthesis of 2-Tyrosyl-3S-tyrosamidomethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride salt **compound #12A**

Step 1

Synthesis of 3-(4-t-butoxy-phenyl)-2S-t-butoxy-carboxamido-1-
[3-(4-t-butoxy-phenyl)-2S-t-butoxy carboxamido propionamido
methyl}-3,4-dihydro-1H-isouquinolin-2-yl]-propan-1-one



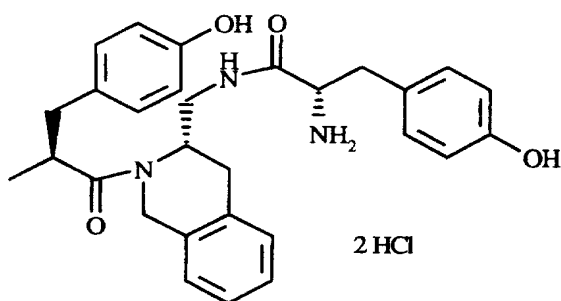
A solution of Boc-Tyr-(t-Bu)-OH (200 mg, 0.592 mmol) in THF (8 ml) was cooled to -10°C and then treated with isobutylchloroformate (81.5 μ l, 0.628 mmol) and subsequently with n-methyl morpholine (69 μ l, 0.628 mmol). After being stirred for 15 minutes, a solution of diamine (67.5 mg, 2.287 mmol) in 2 ml of THF pre-treated with triethyl amine (79.9 μ l, 0.574 mmol), was added. The resulting mixture was stirred for 2 days as it warmed to room temperature. The reaction mixture was evaporated to remove THF and redissolved in ether. The solution was then washed with dilute K₂CO₃ solution and then dried over sodium sulfate. Evaporation of solvent gave a crude product which was chromatographed to give product A (130 mg).

¹H NMR (400 MHz, CDCl₃), δ: 1.26-1.41 (m, 36H, 12xCH₃), 2.57-3.46 (m, 6H, 3xCH₂), 3.92 (br s, 1H, CH), 4.25-4.48 (m, 2H,

CH₂), 4.25 (d, J = 17.4 Hz, 1H), 4.60-4.70 and 4.85-4.96 (m, 1H), 4.83 (q, J = 7.5 Hz, 1H), 5.12 (d, J = 17.4, 1H), 5.25-5.35 (2xd, J = 7.5 Hz, 1H), 5.81 (d, J = 8.0 Hz, 1H), 6.80-7.20 (m, 12H).

Step 2

Synthesis of 2-Tyrosyl-3S-tyrosamidomethyl-1,2,3,4-
5 tetrahydroisoquinoline hydrochloride salt



To a solution of 3-(4-t-butoxy-phenyl)-2S-t-butoxy-
carboxamido-1-[(3-(4-t-butoxy-phenyl)-2S-t-butoxy carboxamido
10 propionamido methyl]-3,4-dihydro-1H-isoquinolin-2-yl]-propan-
1-one (130 mg, 0.162 mmol) in ether (5 ml) was passed a flow
of HCl until a white suspension appeared. The resulting
mixture was stirred for 1 hour as it warmed to room
temperature. Solvent was evaporated to give a white solid
15 which was purified on HPLC (NH₄OAc buffer) to give desired
product as a powder (61.3 mg).

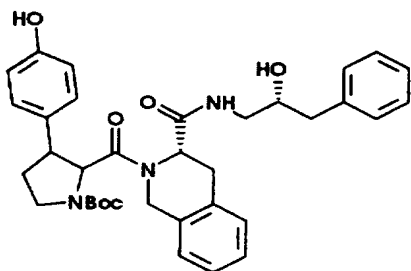
¹H NMR (400 MHz, MeOH-d₄), δ : 1.08 (dd, $J_1 = 17.9$ Hz, $J_2 = 5.0$
Hz, 1H), 2.16 (dd, $J_1 = 17.9$ Hz, $J_2 = 2$ Hz, 1H), 2.75-3.04 (m,
20 6H), 3.54 (tr, $J = 6.0$ Hz, 1H), 4.03 (q, $J = 7.0$ Hz, 1H),
4.28 (d, $J = 18.9$ Hz, 1H), 4.53 (dd, $J_1 = 6.0$ Hz, $J_2 = 9.0$ Hz,
1H), 4.75 (d, $J = 18.9$ Hz, 1H), 6.68 (d, $J = 9.4$ Hz, 2H),
6.75 (d, $J = 9.4$ Hz, 2H), 7.02 (d, $J = 9.4$ Hz, 2H), 7.03 (d,
 $J = 9.4$ Hz, 2H), 6.95-7.20 (m, 5H).

EXAMPLE 7

Synthesis of trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt **compound #14**

Step 1

Synthesis of trans-2-(3S-{[tert-butoxycarbonyl(2R-hydroxy-3-phenyl-propyl)-amino]-methyl-3,4-dihydro-1H-isoquinoline-2-S-carbonyl)-3-(4-hydroxy-phenyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



15

To a solution of trans 3-(4-hydroxy-phenyl)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester which is produced as described in *J. Med. Chem.* **1994**, 37, 4371-4383 (0.10 g, 0.35 mmol), 1,2,3,4-tetrahydro-isoquinoline-3S-carboxylic acid[2R-hydroxy-3-phenyl-propyl]-amide (0.12 g, 0.35 mmol) and DIEA (0.090 g, 0.70 mmol) in DMF (5 mL) was added PyBrOP (0.16 g, 0.35 mmol) under nitrogen at 0°C. After stirring overnight at ambient temperature, the reaction mixture was diluted with ethyl acetate, washed with 10% aqueous KHSO₄, saturated aqueous NaHCO₃, and brine, then dried over MgSO₄, filtered, and concentrated. The residue was chromatographed on silica gel using ethyl acetate/hexane (3:7) as eluant to provide the fast fraction as the TLC fast isomer (0.69 g, 36%) and the slow fraction as the TLC slow isomer (0.75 g, 39%).

30

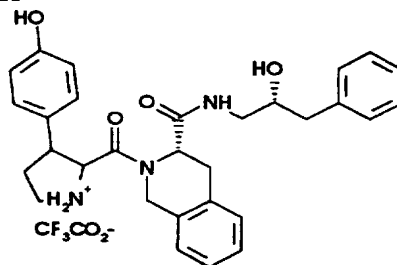
¹H NMR (400 MHz, Bruker, acetone-d₆) (TLC slow isomer) δ: 8.35 (s, 1 H), 7.48 (br, 1 H), 7.20-6.70 (m, 13 H), 5.32 (dd, 1 H, J=1.7 Hz, J=6.5 Hz), 4.83 (d, 1 H, J=15.3 Hz), 4.76 (d, 1 H, J=8.7 Hz), 4.10 (m, 1 H), 3.80 (m, 2 H), 3.60-3.40 (m, 3 H), 3.25 (m, 1 H), 2.85 (m, 1 H), 2.76 (dd, 1 H, J=14.5 Hz, J=5.3 Hz), 2.52 (dd, 1 H, J=13.5 Hz, J=8.2 Hz), 2.25 (m, 2 H), 1.43 (s, 9 H).

¹H NMR (400 MHz, Bruker, acetone-d₆) (TLC fast isomer) δ: 8.53 (m, 1 H), 7.94 (br, 1 H), 7.30-6.70 (, 13 H), 5.00 (m, 1 H), 4.80-4.68 (m, 1 H), 4.25 (m, 1 H), 3.75 (m, 2 H), 3.50 (m, 2 H), 3.45 (m, 1 H), 3.25 (m, 1 H), 3.10 (m, 4 H), 2.55 (m, 2 H), 2.20 (m, 2 H), 1.44 (2s, 9 H).

15

Step 2

Synthesis of trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) **compound #14A**



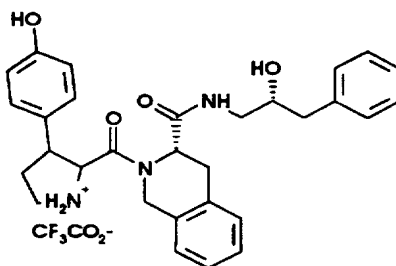
trans-2-(3S-{[tert-Butoxycarbonyl-(2R-hydroxy-3-phenyl-propyl)-amino]-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)-3-(4-hydroxy-phenyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.069 g, 0.12 mmol) was dissolved in 4N HCl in dioxane (5 mL). The solution was stirred at room temperature for 0.5 hr. The solvent was evaporated. The residue was purified by HPLC on a Vydac C18 column under gradient condition [0.1% (W/V) trifluoroacetic acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow

rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.027 g, 38%).

5 LRMS, m/z MH^+ 500.6, $[C_{30}H_{34}N_3O_4]^+$ requires 500.6

Step 2

10 Synthesis of trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **compound #14B**



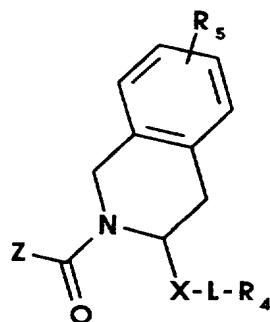
15

Trans-2-(3S-([tert-Butoxycarbonyl-(2R-hydroxy-3-phenyl-propyl)-amino]-methyl-3,4-dihydro-1H-isoquinoline-2-carbonyl)-3-(4-hydroxy-phenyl)-pyrrolidine-1-carboxylic acid
 20 tert-butyl ester (TLC fast isomer)(0.069 g, 0.12 mmol) was dissolved in 4N HCl in dioxane (5 mL). The solution was stirred at room temperature for 0.5 hr. The solvent was evaporated. The residue was purified by HPLC on a Vydac C18 column under gradient condition [0.1% (W/V) trifluoroacetic
 25 acid (TFA) in water/ 0.1% (W/V) TFA in acetonitrile (80/20 to 50/50, flow rate, 3 mL/min], followed by lyophilizing to yield the desire product as white powder (0.028 g, 38%).

LRMS, m/z MH^+ 500.5, $[C_{30}H_{34}N_3O_4]^+$ requires 500.6

We claim:

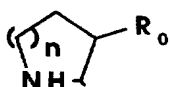
1. An analgesic compound of general formula (I):



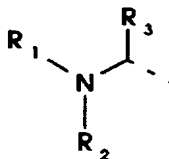
(I)

wherein;

Z is



or



wherein,

n is 1 or 2, and **R₀** is C₆₋₁₂ aryl or C₇₋₁₈ aralkyl; or

R₁ is selected from the group consisting of hydrogen; -NH-C₁₋₆ alkyl; C₁₋₆ alkyl; C₆₋₁₂ aryl; C₇₋₁₈ aralkyl; arginyl; and

R₃₀NHC(=NH)-, wherein,

R₃₀ is hydrogen, C₆₋₁₂ aryl, C₇₋₁₈ aralkyl, or C₁₋₆ alkyl;

R₂ is hydrogen; C₁₋₆ alkyl; or OH;

R₃ is C₆₋₁₂ aryl; or C₇₋₁₈ aralkyl;

R₄ is C₆₋₁₂ aryl; C₇₋₁₈ aralkyl; or C₁₋₁₂ alkyl;

R₅ is C₁₋₆ alkyl; hydrogen; OH; halogen; SH; NO₂; NH₂;

5 -NH-C₁₋₆ alkyl; NH₂C(=NH)-; NH₂C(=NH)-NH-; -COOR₃₁, wherein,
R₃₁ is hydrogen, or C₁₋₆ alkyl;

X is -CH₂NHC(O)-; -CH₂NHC(O)O-; -C(O)NH-; or -CH₂NH-; and

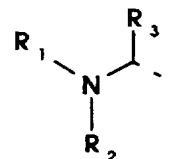
10 **L** is a C₁₋₁₂ alkyl chain which can be substituted with at least one substituent selected from the group consisting of cyclic moiety; C₁₋₆ alkyl; OR₃₁ wherein,

R₃₁ is hydrogen or C₁₋₆ alkyl; SR₃₂ wherein, **R₃₂** is hydrogen or C₁₋₆ alkyl; -NHC(O)**R₃₃** wherein, **R₃₃** is C₆₋₁₂ aryl, C₇₋₁₈ aralkyl or

15 C₁₋₆ alkyl; -OC(O)**R₃₄** wherein, **R₃₄** is hydrogen, C₆₋₁₂ aryl, C₇₋₁₈ aralkyl, C₁₋₆ alkyl, -NHR₃₅ wherein, **R₃₅** is hydrogen, C₆₋₁₂ aryl or C₁₋₆ alkyl; and

NR₆R₇, wherein each of **R₆** and **R₇** is independently hydrogen or C₁₋₆ alkyl;

20



with the proviso that when **R₅** is hydrogen, **Z** is and

X is -C(O)NH-; or -CH₂NH-; that **L** is a C₁₋₁₂ alkyl chain substituted with at least one substituent selected from the group consisting of cyclic moiety; C₁₋₆ alkyl; OR₃₁ wherein,

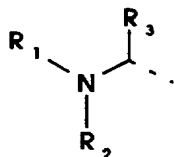
25 **R₃₁** is hydrogen or C₁₋₆ alkyl; SR₃₂ wherein, **R₃₂** is hydrogen or C₁₋₆ alkyl; -NHC(O)**R₃₃** wherein, **R₃₃** is C₆₋₁₂ aryl, C₇₋₁₈ aralkyl or C₁₋₆ alkyl; -OC(O)**R₃₄** wherein, **R₃₄** is hydrogen, C₆₋₁₂ aryl, C₇₋₁₈ aralkyl, C₁₋₆ alkyl, -NHR₃₅ wherein, **R₃₅** is hydrogen, C₆₋₁₂ aryl

or C₁₋₆ alkyl; and

NR₆R₇, wherein each of R₆ and R₇ is independently hydrogen or C₁₋₆ alkyl.

5

2. An analgesic compound according to claim 1 wherein;



Z is , wherein each of R₁, R₂, and R₃ are as defined in claim 1.

10

3. An analgesic compound according to claim 1 or claim 2 wherein;

15 R₁ is hydrogen; NH₂C(=NH)-; or C₁₋₆ alkyl;

R₂ is hydrogen or -CH₃; and

R₃ is preferably selected from the group consisting of:

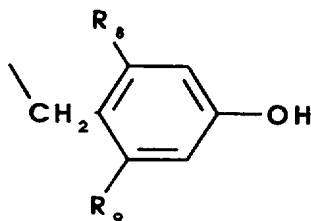
-CH₂-C₆H₂R₈R₉-, or -CH₂-HOC₆HR₈R₉, wherein each of R₈ and R₉ is independently -CH₃ or hydrogen.

20

4. An analgesic compound according to claim 3 wherein;

R₁ is hydrogen; NH₂C(=NH)-; or -CH₃;

R₂ is hydrogen; and



25 R₃ is ;

wherein each of **R₈** and **R₉** is independently -CH₃ or hydrogen.

5. An analgesic compound according to claim 4 wherein;

5

R₈ and **R₉** are CH₃.

6. An analgesic compound according to anyone of claims 1 to 5
10 wherein;

X is -C(O)NH-; or -CH₂NH-.

7. An analgesic compound according to anyone of claims 1 to 5
15 wherein **X** is -C(O)NH-.

8. An analgesic compound according to anyone of claims 1 to 5
wherein **L** is -(CH₂)₁₋₃-CH**R₁₀**-(CH₂)₁₋₃-, wherein **R₁₀** is OH, or
20 NH₂.

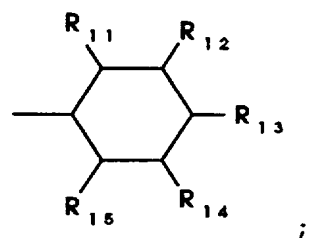
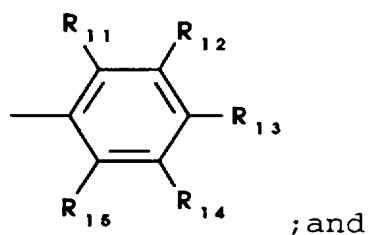
9. An analgesic compound according to anyone of claims 1 to 5
wherein **L** is -(CH₂)-CH**R₁₀**-(CH₂)-, wherein **R₁₀** is OH, or NH₂.

25 10. An analgesic compound according to anyone of claims 1 to 5
wherein **L** is more preferably -(CH₂)-CHOH-(CH₂)-.

11. An analgesic compound according to anyone of claims 1 to
30 10 wherein:

R₄ is selected from the group consisting of:

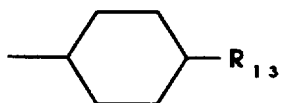
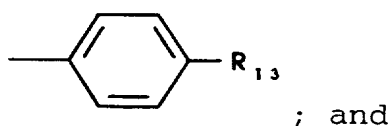
C₁₋₁₂ alkyl;



5 wherein each of **R₁₁**, **R₁₂**, **R₁₃**, **R₁₄**, and **R₁₅** is independently CH₃, hydrogen, halogen, OH, SH, NH₂, or NO₂.

12. An analgesic compound according to anyone of claims 1 to
10 wherein;

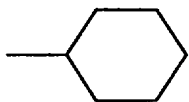
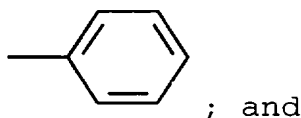
R₄ is selected from the group consisting of: -CH₃; -C(CH₃)₃;
-CH(CH₃)₂;



15 wherein **R₁₃** is as defined above.

13. An analgesic compound according to anyone of claims 1 to
20 wherein;

R₄ is selected from the group consisting of:



5

14. An analgesic compound selected from the group consisting of :

2-R-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
10 hydroxy-3-phenyl-propyl)amide trifluoroacetic salt
(racemic mixture) **compound #1**;

2-R-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast
15 isomer) **compound #1A**; 2-R-(2-Amino-3-(4-hydroxy-2,6-
dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-
isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-
propyl)amide trifluoroacetic salt (slow isomer) **Compound**

1B; 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-
20 propionyl)-7-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-S-
carboxylic acid (2-hydroxy-3-phenyl-propyl)amide
trifluoroacetic salt (racemic mixture) **compound #2**; 2-(2-
Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-
25 hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt
(racemic mixture) **compound #3**;

2-(2-Guanidino-3-(4-
hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-
tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-
3-phenyl-propyl)-amide ditrifluoroacetic salt (fast isomer)
30 **compound #3A**; 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-
phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-

carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide
ditrifluoroacetic salt (slow isomer) **compound #3B**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
5 hydroxy-3-phenyl-propyl)amide trifluoroacetic salt
(racemic mixture) of **compound #4**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast
10 isomer) of **compound # 4A**;

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow
isomer) **Compound #4B**;

15 S-2-(2-Amino-3-(hydroxy-phenyl)-S-1,2,3,4-
tetrahydroisoquinoline-carboxylic acid (R-2-hydroxy-3-
phenyl-propyl)-amide hydrochloride acid (racemic mixture)
compound #8;

S-2-(2-Amino-3-(hydroxy-phenyl)-S-1,2,3,4-
20 tetrahydroisoquinoline-carboxylic acid (R-2-hydroxy-3-
phenyl-propyl)-amide hydrochloride acid (slow isomer)
compound #8a;

2-S-Amino- 3-(4-hydroxy-phenyl)-1-{3-(R-2-hydroxy-3-
phenyl-propylamino)-methyl}-S-3,4-dihydro-1H-isoquinolin-
25 2-yl}propan-1-one ditrifluoroacetic salt (fast isomer)
compound #9A ;

2-(tyrosyl)-3S-(D-phenylalanamido methyl)-1,2,3,4-
tetrahydro isoquinoline hydro chloride salt **compound #10A**;

2-(tyrosyl)-3S-phenylalanamido methyl)-1,2,3,4-tetrahydro
30 isoquinoline hydro chloride salt **compound #11A**;

2-Tyrosyl-3S-tyrosamidomethyl-1,2,3,4-
tetrahydroisoquinoline hydrochloride salt **compound #12A**;

2-Tyrosyl-3-benzoxycarboxamidomethyl-1,2,3,4-
tetrahydroisoquinoline hydrochloride salt **compound #13A**;

trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt

compound #14;

5 trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) **compound #14A;** trans-2-(3-(4-hydroxy-phenyl)-pyrrolidine-2-carbonyl-S-1,2,3,4-tetrahydroquinoline-3-
10 carboxylic acid (R-2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **compound #14B;**

and pharmaceutically acceptable derivatives thereof.

15 15. An analgesic compound selected from the group consisting of:

2-R-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
20 hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow isomer) **Compound 1B;** 2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-7-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture)

25 **compound #2;** 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt (fast isomer) **compound #3A;** 2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
30 1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic salt (slow isomer) **compound #3B;**

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
35 hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (fast isomer) of **compound #4A ;**

2-S-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
hydroxy-3-phenyl-propyl)amide trifluoroacetic salt (slow
isomer) **Compound #4B**;

5 and pharmaceutically acceptable derivatives thereof.

16. An analgesic compound:

2-(2-Guanidino-3-(4-hydroxy-2,6-dimethyl-phenyl)-
10 propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic
acid (2-R-hydroxy-3-phenyl-propyl)-amide ditrifluoroacetic
salt (fast isomer) **compound #3a**; and pharmaceutically
acceptable derivatives thereof.

15

17. A pharmaceutically acceptable composition comprising an
analgesic compound according to anyone of claims 1 to 16,
for use in the treatment of pain.

20

18. The use of an analgesic compound as described in claim 1
wherein;

25

L is a C₁₋₁₂ alkyl chain which can be substituted with at
least one substituent selected from the group consisting
of cyclic moiety; C₁₋₆ alkyl; OR₃₁ wherein,

R₃₁ is hydrogen or C₁₋₆ alkyl; SR₃₂ wherein, **R₃₂** is hydrogen
or C₁₋₆ alkyl; -NHC(O)**R₃₃** wherein, **R₃₃** is C₆₋₁₂ aryl, C₇₋₁₈

30

aralkyl or C₁₋₆ alkyl; -OC(O)**R₃₄** wherein, **R₃₄** is hydrogen, C₆₋₁₂
aryl, C₇₋₁₈ aralkyl, C₁₋₆ alkyl, -NHR₃₅ wherein, **R₃₅** is
hydrogen, C₆₋₁₂ aryl or C₁₋₆ alkyl; and

NR₆R₇, wherein each of **R₆** and **R₇** is independently hydrogen
or C₁₋₆ alkyl; for the manufacture of peripheral analgesic
for the treatment of pain.

19. The use according to claim 18 wherein the analgesic compound is selected from the group consisting of:

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture)
compound #5;

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (fast isomer)
compound #5a;

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt **compound #5b;**

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (racemic mixture)
compound #6;

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (fast isomer)
compound #6A; and

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-phenyl-propyl)amide trifluoroacetic salt (slow isomer)
compound #6B;

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (racemic mixture) **compound #7**

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (fast

isomer) **compound #7A**;

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (slow

5 isomer) **compound #7B**;

and pharmaceutically acceptable derivatives thereof.

20. The use according to claim 18 wherein the analgesic
compound is selected from the group consisting of:

10

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt (fast isomer)

compound #5A; and

15

2-(2-Amino-3-(4-Hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (3-
phenyl-propyl)amide trifluoroacetic salt **compound #5B**;

20

2-(2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl)-
1,2,3,4-tetrahydro-isoquinoline-3-S-carboxylic acid (2-
fluoro-(4-phenyl-ethyl)amide trifluoroacetic salt (fast
isomer) **compound #7A**;

and pharmaceutically acceptable derivatives thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00315

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07K 5/065, A61K 38/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REG, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Analgesia, Volume 1, No 4-6, 1995, P.W. Schiller et al, "Four different types of opioid peptides with mixed u agonist/alpha antagonist properites" page 703 - page 706 --	1-20
P,X	WO 9606855 A1 (ASTRA AKTIEBOLAG), 7 March 1996 (07.03.96) --	1-20
A	WO 9415959 A1 (AKTIEBOLAGET ASTRA), 21 July 1994 (21.07.94) -- -----	1-20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

19 June 1997

Date of mailing of the international search report

24.06.97

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INTERNATIONAL SEARCH REPORT

Information on patent family members

03/06/97

International application No.

PCT/SE 97/00315

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